

University of Dundee

Interventions for preventing oral mucositis in patients with cancer receiving treatment

Riley, Philip; Glenny, Anne Marie; Worthington, Helen V.; Littlewood, Anne; Fernandez Mauleffinch, Luisa M.; Clarkson, Jan E.

Published in:
Cochrane Database of Systematic Reviews

DOI:
[10.1002/14651858.CD011990.pub2](https://doi.org/10.1002/14651858.CD011990.pub2)

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):
Riley, P., Glenny, A. M., Worthington, H. V., Littlewood, A., Fernandez Mauleffinch, L. M., Clarkson, J. E., & McCabe, M. G. (2017). Interventions for preventing oral mucositis in patients with cancer receiving treatment: Cytokines and growth factors. *Cochrane Database of Systematic Reviews*, 2017(11), 1-194. [CD011990]. <https://doi.org/10.1002/14651858.CD011990.pub2>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.



Cochrane
Library

Cochrane Database of Systematic Reviews

Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors (Review)

Riley P, Glenny AM, Worthington HV, Littlewood A, Fernandez Mauleffinch LM, Clarkson JE, McCabe MG

Riley P, Glenny AM, Worthington HV, Littlewood A, Fernandez Mauleffinch LM, Clarkson JE, McCabe MG.

Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors.

Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD011990.

DOI: 10.1002/14651858.CD011990.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	7
OBJECTIVES	8
METHODS	8
RESULTS	11
Figure 1.	13
Figure 2.	21
ADDITIONAL SUMMARY OF FINDINGS	27
DISCUSSION	33
AUTHORS' CONCLUSIONS	35
ACKNOWLEDGEMENTS	36
REFERENCES	36
CHARACTERISTICS OF STUDIES	44
DATA AND ANALYSES	132
Analysis 1.1. Comparison 1 KGF versus placebo, Outcome 1 Oral mucositis (any).	139
Analysis 1.2. Comparison 1 KGF versus placebo, Outcome 2 Oral mucositis (moderate + severe).	140
Analysis 1.3. Comparison 1 KGF versus placebo, Outcome 3 Oral mucositis (severe).	141
Analysis 1.4. Comparison 1 KGF versus placebo, Outcome 4 Interruptions to cancer treatment (unscheduled RT breaks of 5 or more days).	142
Analysis 1.5. Comparison 1 KGF versus placebo, Outcome 5 Interruptions to cancer treatment (chemotherapy delays/discontinuations).	143
Analysis 1.6. Comparison 1 KGF versus placebo, Outcome 6 Oral pain.	144
Analysis 1.7. Comparison 1 KGF versus placebo, Outcome 7 Normalcy of diet (use of supplemental nutrition).	145
Analysis 1.8. Comparison 1 KGF versus placebo, Outcome 8 Normalcy of diet (worst ability to eat score - 1 to 4 scale).	146
Analysis 1.9. Comparison 1 KGF versus placebo, Outcome 9 Number of days in hospital.	146
Analysis 1.10. Comparison 1 KGF versus placebo, Outcome 10 Number of days of treatment with opioid analgesics.	147
Analysis 2.1. Comparison 2 KGF (dose comparison), Outcome 1 Oral mucositis (any).	147
Analysis 2.2. Comparison 2 KGF (dose comparison), Outcome 2 Oral mucositis (moderate + severe).	148
Analysis 2.3. Comparison 2 KGF (dose comparison), Outcome 3 Oral mucositis (severe).	149
Analysis 2.4. Comparison 2 KGF (dose comparison), Outcome 4 Oral pain (maximum score on 0 to 10 VAS).	149
Analysis 2.5. Comparison 2 KGF (dose comparison), Outcome 5 Normalcy of diet (use of TPN).	150
Analysis 2.6. Comparison 2 KGF (dose comparison), Outcome 6 Normalcy of diet (worst ability to eat score - 1 to 4 scale).	150
Analysis 2.7. Comparison 2 KGF (dose comparison), Outcome 7 Number of days in hospital.	151
Analysis 2.8. Comparison 2 KGF (dose comparison), Outcome 8 Number of days of treatment with opioid analgesics.	152
Analysis 3.1. Comparison 3 KGF versus chlorhexidine, Outcome 1 Oral mucositis (any).	152
Analysis 3.2. Comparison 3 KGF versus chlorhexidine, Outcome 2 Oral mucositis (moderate + severe).	153
Analysis 3.3. Comparison 3 KGF versus chlorhexidine, Outcome 3 Oral mucositis (severe).	153
Analysis 4.1. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 1 Oral mucositis (any).	154
Analysis 4.2. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 2 Oral mucositis (moderate + severe).	155
Analysis 4.3. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 3 Oral mucositis (severe).	156
Analysis 4.4. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 4 Oral pain (maximum score on 0 to 10 VAS).	157
Analysis 4.5. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 5 Normalcy of diet (use of feeding tube/parenteral nutrition).	158
Analysis 4.6. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 6 Number of days of treatment with opioid analgesics.	159
Analysis 5.1. Comparison 5 GM-CSF (dose comparison), Outcome 1 Oral mucositis (severe).	159

Analysis 6.1. Comparison 6 GM-CSF versus sucralfate, Outcome 1 Oral mucositis (moderate + severe).	160
Analysis 6.2. Comparison 6 GM-CSF versus sucralfate, Outcome 2 Oral mucositis (severe).	161
Analysis 6.3. Comparison 6 GM-CSF versus sucralfate, Outcome 3 Interruptions to cancer treatment.	161
Analysis 6.4. Comparison 6 GM-CSF versus sucralfate, Outcome 4 Normalcy of diet (use of PEG tube).	162
Analysis 7.1. Comparison 7 G-CSF versus placebo/no treatment, Outcome 1 Oral mucositis (any).	163
Analysis 7.2. Comparison 7 G-CSF versus placebo/no treatment, Outcome 2 Oral mucositis (moderate + severe).	164
Analysis 7.3. Comparison 7 G-CSF versus placebo/no treatment, Outcome 3 Oral mucositis (severe).	164
Analysis 7.4. Comparison 7 G-CSF versus placebo/no treatment, Outcome 4 Interruptions to cancer treatment (RT interruption).	165
Analysis 7.5. Comparison 7 G-CSF versus placebo/no treatment, Outcome 5 Normalcy of diet (use of PEG tube).	166
Analysis 8.1. Comparison 8 G-CSF (pegfilgrastim) versus G-CSF (filgrastim), Outcome 1 Oral mucositis (any).	166
Analysis 8.2. Comparison 8 G-CSF (pegfilgrastim) versus G-CSF (filgrastim), Outcome 2 Oral mucositis (moderate + severe).	167
Analysis 8.3. Comparison 8 G-CSF (pegfilgrastim) versus G-CSF (filgrastim), Outcome 3 Normalcy of diet (use of supplemental nutrition).	168
Analysis 9.1. Comparison 9 EGF versus placebo, Outcome 1 Oral mucositis (moderate + severe).	169
Analysis 9.2. Comparison 9 EGF versus placebo, Outcome 2 Oral mucositis (severe).	170
Analysis 9.3. Comparison 9 EGF versus placebo, Outcome 3 Interruptions to cancer treatment (RT breaks > 2 consecutive days).	170
Analysis 9.4. Comparison 9 EGF versus placebo, Outcome 4 Normalcy of diet (use of supplemental nutrition).	171
Analysis 10.1. Comparison 10 ITF versus placebo, Outcome 1 Oral mucositis (any).	171
Analysis 10.2. Comparison 10 ITF versus placebo, Outcome 2 Oral mucositis (moderate + severe).	172
Analysis 10.3. Comparison 10 ITF versus placebo, Outcome 3 Oral mucositis (severe).	172
Analysis 11.1. Comparison 11 ITF (dose comparison), Outcome 1 Oral mucositis (any).	173
Analysis 11.2. Comparison 11 ITF (dose comparison), Outcome 2 Oral mucositis (moderate + severe).	173
Analysis 11.3. Comparison 11 ITF (dose comparison), Outcome 3 Oral mucositis (severe).	174
Analysis 12.1. Comparison 12 Erythropoietin versus placebo, Outcome 1 Oral mucositis (any).	174
Analysis 12.2. Comparison 12 Erythropoietin versus placebo, Outcome 2 Oral mucositis (moderate + severe).	175
Analysis 12.3. Comparison 12 Erythropoietin versus placebo, Outcome 3 Oral mucositis (severe).	175
Analysis 12.4. Comparison 12 Erythropoietin versus placebo, Outcome 4 Number of days in hospital.	176
ADDITIONAL TABLES	176
APPENDICES	181
HISTORY	192
CONTRIBUTIONS OF AUTHORS	192
DECLARATIONS OF INTEREST	193
SOURCES OF SUPPORT	193
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	194

Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Philip Riley¹, Anne-Marie Glenny², Helen V Worthington¹, Anne Littlewood¹, Luisa M Fernandez Mauleffinch¹, Jan E Clarkson³, Martin G McCabe⁴

¹ Cochrane Oral Health, Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK. ² Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK. ³ Division of Oral Health Sciences, University of Dundee, Dundee, UK. ⁴ Division of Cancer Sciences, The University of Manchester, Manchester, UK

Contact address: Philip Riley, Cochrane Oral Health, Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, JR Moore Building, Oxford Road, Manchester, M13 9PL, UK. philip.riley@manchester.ac.uk.

Editorial group: Cochrane Oral Health Group.

Publication status and date: New, published in Issue 11, 2017.

Citation: Riley P, Glenny AM, Worthington HV, Littlewood A, Fernandez Mauleffinch LM, Clarkson JE, McCabe MG. Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD011990. DOI: 10.1002/14651858.CD011990.pub2.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Oral mucositis is a side effect of chemotherapy, head and neck radiotherapy, and targeted therapy, affecting over 75% of high-risk patients. Ulceration can lead to severe pain and difficulty with eating and drinking, which may necessitate opioid analgesics, hospitalisation and supplemental nutrition. These complications may disrupt cancer therapy, which may reduce survival. There is also a risk of death from sepsis if pathogens enter the ulcers of immunocompromised patients. Ulcerative oral mucositis can be costly to healthcare systems, yet there are few preventive interventions proven to be beneficial. Cytokines and growth factors may help the regeneration of cells lining of the mouth, thus preventing or reducing oral mucositis and its negative effects.

Objectives

To assess the effects of cytokines and growth factors for preventing oral mucositis in patients with cancer who are receiving treatment.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (searched 10 May 2017); the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 4) in the Cochrane Library (searched 10 May 2017); MEDLINE Ovid (1946 to 10 May 2017); Embase Ovid (7 December 2015 to 10 May 2017); CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 10 May 2017); and CANCERLIT PubMed (1950 to 10 May 2017). The US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) and the [World Health Organization International Clinical Trials Registry Platform](http://www.who.int/trials/registry) were searched for ongoing trials.

Selection criteria

We included parallel-design randomised controlled trials (RCTs) assessing the effects of cytokines and growth factors in patients with cancer receiving treatment.

Data collection and analysis

Two review authors independently screened the results of electronic searches, extracted data and assessed risk of bias. For dichotomous outcomes, we reported risk ratios (RR) and 95% confidence intervals (CI). For continuous outcomes, we reported mean differences (MD) and 95% CIs. We pooled similar studies in random-effects meta-analyses. We reported adverse effects in a narrative format.

Main results

We included 35 RCTs analysing 3102 participants. Thirteen studies were at low risk of bias, 12 studies were at unclear risk of bias, and 10 studies were at high risk of bias.

Our main findings were regarding keratinocyte growth factor (KGF) and are summarised as follows.

There might be a reduction in the risk of moderate to severe oral mucositis in adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers (RR 0.89, 95% CI 0.80 to 0.99; 6 studies; 852 participants; low-quality evidence). We would need to treat 11 adults with KGF in order to prevent one additional adult from developing this outcome (95% CI 6 to 112). There might be a reduction in the risk of severe oral mucositis in this population, but there is also some possibility of an increase in risk (RR 0.85, 95% CI 0.65 to 1.11; 6 studies; 852 participants; low-quality evidence). We would need to treat 10 adults with KGF in order to prevent one additional adult from developing this outcome (95% CI 5 to prevent the outcome to 14 to cause the outcome).

There is probably a reduction in the risk of moderate to severe oral mucositis in adults receiving radiotherapy to the head and neck with cisplatin or fluorouracil (RR 0.91, 95% CI 0.83 to 1.00; 3 studies; 471 participants; moderate-quality evidence). We would need to treat 12 adults with KGF in order to prevent one additional adult from developing this outcome (95% CI 7 to infinity). It is very likely that there is a reduction in the risk of severe oral mucositis in this population (RR 0.79, 95% CI 0.69 to 0.90; 3 studies; 471 participants; high-quality evidence). We would need to treat 7 adults with KGF in order to prevent one additional adult from developing this outcome (95% CI 5 to 15).

It is likely that there is a reduction in the risk of moderate to severe oral mucositis in adults receiving chemotherapy alone for mixed solid and haematological cancers (RR 0.56, 95% CI 0.45 to 0.70; 4 studies; 344 participants; moderate-quality evidence). We would need to treat 4 adults with KGF in order to prevent one additional adult from developing this outcome (95% CI 3 to 6). There might be a reduction in the risk of severe oral mucositis in this population (RR 0.30, 95% CI 0.14 to 0.65; 3 studies; 263 participants; low-quality evidence). We would need to treat 10 adults with KGF in order to prevent one additional adult from developing this outcome (95% CI 8 to 19).

Due to the low volume of evidence, single-study comparisons and insufficient sample sizes, we found no compelling evidence of a benefit for any other cytokines or growth factors and there was no evidence on children. There did not appear to be any serious adverse effects of any of the interventions assessed in this review.

Authors' conclusions

We are confident that KGF is beneficial in the prevention of oral mucositis in adults who are receiving: a) radiotherapy to the head and neck with cisplatin or fluorouracil; or b) chemotherapy alone for mixed solid and haematological cancers. We are less confident about a benefit for KGF in adults receiving bone marrow/stem cell transplant after conditioning therapy for haematological cancers because of multiple factors involved in that population, such as whether or not they received total body irradiation (TBI) and whether the transplant was autologous (the patients' own cells) or allogeneic (cells from a donor). KGF appears to be a relatively safe intervention.

Due to limited research, we are not confident that there are any beneficial effects of other cytokines and growth factors. There is currently insufficient evidence to draw any conclusions about the use of cytokines and growth factors in children.

PLAIN LANGUAGE SUMMARY

Can cytokines and growth factors help prevent mouth soreness and ulcers (oral mucositis) in patients being treated for cancer?

Review question

This review has been produced to assess whether or not the use of cytokines and growth factors during cancer treatment, can help prevent mouth soreness and ulcers.

Background

Sore mouth and ulcers (oral mucositis) is a side effect of treatment for cancer including chemotherapy, head and neck radiotherapy, and targeted therapy, affecting over 75% of high-risk patients. Ulcers can lead to severe pain and difficulty with eating and drinking. Sufferers may need strong painkillers, possibly have to go into hospital and even be fed through a tube into their stomach or their veins.

These complications may disrupt their cancer therapy, meaning they are not receiving the best treatment, which may reduce survival. Cancer patients have weakened immune systems due to their treatment and are less able to fight infections. An ulcer is an open wound and there is a risk that bacteria can enter the body leading to infection or sepsis (a dangerous inflammatory reaction of the body to infection).

Mouth soreness and ulcers can be costly to healthcare systems, yet there are few preventive interventions or treatments proven to be beneficial. Cytokines and growth factors may help the regeneration of cells lining the mouth, thus preventing or reducing oral mucositis and its negative effects.

Study characteristics

Authors from [Cochrane Oral Health](#) carried out this review of existing studies and the evidence is current up to 10 May 2017. It includes 35 studies (published between 1993 and 2017) with 3102 participants, all patients being treated for cancer, aged from 1 to 87 years old. Review authors included studies comparing cytokines and growth factors for the prevention of oral mucositis. The studies were carried out all over the world and often featured multiple sites, although most took place in high-income countries.

Main results

The main findings were regarding keratinocyte growth factor (KGF). KGF is likely to reduce the risk of oral mucositis in adults who are receiving either radiotherapy to the head and neck with chemotherapy (cisplatin or fluorouracil), or chemotherapy alone for mixed solid and blood cancers. KGF may also reduce the risk of oral mucositis in adults receiving bone marrow/stem cell transplant after conditioning therapy for blood cancers, but these results are less clear because of multiple complicating factors. KGF appears to be a relatively safe intervention. There did not appear to be any serious adverse effects of any of the interventions assessed in this review.

Due to limited research, review authors are uncertain of any beneficial effects of other cytokines and growth factors. There is currently insufficient evidence to draw any conclusions about the use of cytokines and growth factors in children.

Quality of the evidence

For reducing oral mucositis in adults receiving radiotherapy to the head and neck with chemotherapy, review authors rated the evidence for KGF as moderate to high quality. For reducing oral mucositis in adults receiving chemotherapy alone for mixed solid and blood cancers, they rated the evidence for KGF as low to moderate quality. This evidence was downgraded due to there not being enough data and because some results have not yet been published. For reducing oral mucositis in adults receiving bone marrow/stem cell transplant after conditioning therapy for blood cancers, they rated the evidence for KGF as low quality because results were not similar across the studies and some results have not yet been published. Evidence on side effects of KGF was poorly reported and inconsistent.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

KGF compared to placebo for preventing oral mucositis in adults with cancer receiving treatment						
Patient or population: adults** receiving treatment for cancer (see subgroup for treatment type) Setting: hospital Intervention: KGF Comparison: placebo						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with KGF				
Oral mucositis (moderate + severe)	BMT/SCT after conditioning for haematological cancers		RR 0.89 (0.80 to 0.99)	852 (6 studies)	⊕⊕○○ LOW ¹	There might be a benefit for KGF in this population NNTB = 11 (95% CI 6 to 112)
	848 per 1000	755 per 1000 (678 to 839)				
	RT to head and neck with cisplatin/5FU		RR 0.91 (0.83 to 1.00)	471 (3 studies)	⊕⊕⊕○ MODERATE ²	There is probably a benefit for KGF in this population NNTB = 12 (95% CI 7 to)
	932 per 1000	848 per 1000 (773 to 932)				
	CT alone for mixed cancers		RR 0.56 (0.45 to 0.70)	344 (4 studies)	⊕⊕⊕○ MODERATE ³	It is likely that there is a benefit for KGF in this population NNTB = 4 (95% CI 3 to 6)
	631 per 1000	353 per 1000 (284 to 441)				
Oral mucositis (severe)	BMT/SCT after conditioning for haematological cancers		RR 0.85 (0.65 to 1.11)	852 (6 studies)	⊕⊕○○ LOW ⁴	There might be a benefit for KGF in this population, but there is also some possibility of an increase in risk

	677 per 1000	575 per 1000 (440 to 751)			
	RT to head and neck with cisplatin/5FU		RR 0.79 (0.69 to 0.90)	471 (3 studies)	⊕⊕⊕⊕ HIGH
	700 per 1000	553 per 1000 (483 to 630)			It is very likely that there is a benefit for KGF in this population NNTB = 7 (95% CI 5 to 15)
	CT alone for mixed cancers		RR 0.30 (0.14 to 0.65)	263 (3 studies)	⊕⊕○○ LOW ⁵
	154 per 1000	46 per 1000 (22 to 100)			There might be a benefit for KGF in this population NNTB = 10 (95% CI 8 to 19)
Adverse events	Adverse events that were attributed to the study drugs rather than the cancer therapy were typically oral-related or skin-related. Events were mostly mild to moderate with very few incidences of serious events. However, reporting was poor and inconsistent, meaning that it was not appropriate to meta-analyse data				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**Only 1 study in the subgroup BMT/SCT after conditioning for haematological cancers' included some children (but the median age of participants was 46 years)

***The number of people that would need to receive KGF in order to prevent 1 additional person from developing the outcome. Calculated as 1 divided by the absolute risk reduction (which is the control arm event rate minus the experimental arm event rate). NNTH means the number of people that would need to receive KGF to cause 1 additional person to develop the outcome. All decimal places have been rounded up to the nearest whole number (i.e. 6.1 = 7).

: infinity; **5FU**: fluorouracil; **BMT**: bone marrow transplantation; **CI**: confidence interval; **CT**: chemotherapy; **KGF**: keratinocyte growth factor; **NNTB**: number needed to treat to benefit***; **NNTH**: number needed to treat to harm; **RR**: risk ratio; **RT**: radiotherapy; **SCT**: stem cell transplantation.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Downgraded by 1 level for inconsistency (substantial heterogeneity: $I^2 = 50\%$ to 90% , $P < 0.1$); downgraded 1 further level for publication bias as there are 2 references in [Studies awaiting classification](#) that would be included in the conditioning/transplant subgroup, but the data are not available ([NCT02313792](#); [Spielberger 2001](#)).

²Downgraded by 1 level for inconsistency (substantial heterogeneity: $I^2 = 50\%$ to 90% , $P < 0.1$).

³Downgraded by 1 level for publication bias as there is 1 reference in [Studies awaiting classification](#) that would be included in the chemotherapy alone subgroup, but the data are not available ([NCT00393822](#)).

⁴Downgraded by 1 level for inconsistency (substantial heterogeneity: $I^2 = 50\%$ to 90% , $P < 0.1$); downgraded 1 further level for publication bias as there are 2 references in [Studies awaiting classification](#) that would be included in the conditioning/transplant subgroup, but the data are not available ([NCT02313792](#); [Spielberger 2001](#)); we did not downgrade for imprecision because, despite the confidence interval including a small chance of an increase in risk, it is a fairly narrow interval and a rating of 'very low quality' would seem an overly harsh rating for this body of evidence.

⁵Downgraded by 1 level for imprecision (wide confidence interval, small sample size and low event rate); downgraded 1 further level for publication bias as there is 1 reference in [Studies awaiting classification](#) that would be included in the chemotherapy alone subgroup, but the data are not available ([NCT00393822](#)).

BACKGROUND

Description of the condition

Treating cancer with chemotherapy, radiotherapy of the head and neck, or targeted therapy can cause toxic oral side effects (Al-Dasooqi 2013; Scully 2006; Sonis 2004). Perhaps the most widely researched of these side effects is oral mucositis (Al-Dasooqi 2013), which affects at least 75% of high risk patients (those receiving head and neck radiotherapy or high-dose chemotherapy) (Scully 2006). Oral mucositis may be under-reported in lower risk groups for various reasons: their tendency to be outpatients with less observation; less reporting of moderate mucositis; or patients and clinicians wishing to avoid any disruption to optimal cancer treatment (Scully 2006).

Simply put, oral mucositis affects the oral mucosa (the mucous membrane of moist tissue lining the oral cavity) and can lead to the development of lesions (ulcers). However, the process that leads to oral mucositis is complex and multifactorial, with Sonis' five-phase model being a widely accepted description of the sequence of events underlying the condition (Sonis 2004; Sonis 2009).

1. Initiation: DNA damage caused by chemotherapy or radiotherapy results in the loss of ability to proliferate in the basal cells of the epithelium (the external layers of cells lining the oral mucosa). This produces reactive oxygen species (ROS).

2. Primary damage response: radiotherapy, chemotherapy, ROS, and DNA strand breaks all contribute to the activation of transcription factors such as nuclear factor kappa beta (NF- κ B), and sphingomyelinases. All this leads to the upregulation of pro-inflammatory cytokines (e.g. tumour necrosis factor alpha - TNF- α), nitric oxide, ceramide, and matrix metalloproteinases, resulting in the thinning of the epithelium through tissue injury and cell death, culminating with the destruction of the oral mucosa.

3. Signal amplification: some of the molecules in the previous phase can lead to the exacerbation and prolonging of tissue injury through positive or negative feedback (e.g. TNF- α can positively feedback on NF- κ B thus inducing more pro-inflammatory cytokine production).

4. Ulceration: bacteria colonise ulcers and their cell wall products infiltrate the submucosa (the connective tissues beneath the oral mucosa), activating tissue macrophages (white blood cells that respond to infection or damaged/dead cells), which results in further production of pro-inflammatory cytokines, inflammation, and pain.

5. Healing: signalling from the extracellular matrix of the submucosa results in epithelial proliferation and differentiation, and thus a thickening of the epithelium. The local oral flora are reinstated.

However, there remains a lack of clarity around mechanisms and risk factors for oral mucositis, particularly areas such as genetic predisposition and microbial effects. Understanding of the patho-

biology leading to mucosal toxicity as a result of targeted therapies (e.g. mammalian target of rapamycin (mTOR) inhibitor-associated stomatitis - mIAS) is also currently limited, but it is thought to differ from chemotherapy- and radiotherapy-induced mucositis, and the clinical presentation of the ulcers is more similar to aphthous stomatitis (Al-Dasooqi 2013; Boers-Doets 2013; Peterson 2015).

Oral mucositis is an acute condition and, when caused by chemotherapy, ulceration normally occurs one week after treatment and resolves within three weeks of treatment (Sonis 2009). Radiotherapy-induced oral mucositis takes longer both to develop and to heal, with ulceration normally occurring around two weeks into a seven-week treatment cycle, and resolving three to four weeks after treatment has ended (Sonis 2009).

Ulceration is the most significant phase as it leads to pain of varying severity, and difficulties with eating, swallowing, and talking (Scully 2006). This in turn leads to the consumption of pain relief medication, nutritional support (i.e. nasogastric or intravenous feeding), treatment of the oral mucositis, specialist oral hygiene care, increased medical appointments and use of staff and resources, and, in some instances, hospitalisation (Jensen 2014; Miller 2001; Trotti 2003). Thus the negative impact on the quality of life of cancer patients, when they are already suffering, is severe (Elting 2008; Epstein 1999). Further problems can occur in immunosuppressed patients if whole bacteria on the ulcer surface cross into the underlying submucosa, potentially leading to bacteraemia and sepsis, which require antibiotics and hospitalisation, and can cause death (Jensen 2014; Peterson 2015; Scully 2006). Therefore, oral mucositis can be a dose-limiting condition, disrupting a patient's optimal cancer treatment plan (Jensen 2014; Peterson 2015; Sonis 2004). The additional costs associated with oral mucositis are significant, with one study reporting a median incremental cost of USD 18,515 per patient (Nonzee 2008). These costs have been reported to be as much as USD 42,749 more per patient when ulcerative oral mucositis is present (Sonis 2001).

Description of the intervention

As described above, oral mucositis occurs partly as result of the loss of regenerative ability of the oral epithelial cells. Growth factors and anti-inflammatory cytokines are used to counteract the biological processes leading to this loss of proliferative ability. Growth factors and anti-inflammatory cytokines include (Raber-Durlacher 2013):

- keratinocyte growth factor;
- colony-stimulating factors;
- epidermal growth factor;
- transforming growth factor-beta;
- whey-derived growth factor;
- interleukin-11;
- ATL-104;
- trefoil factor.

How the intervention might work

The growth factors described here are proteins that bind to receptors of target cells and either increase the proliferation of the epithelial cells that form the mucous membrane lining of the oral cavity, or promote the recovery of the white blood cells that contribute to the maintenance of oral health following conventional or high dose chemotherapy (with or without radiotherapy) (Raber-Durlacher 2013). Anti-inflammatory cytokines are also proteins or glycoproteins that bind to receptors of target cells, and are thought to alter the complex balance of pro- and anti-inflammatory cytokines involved in the pathogenesis of oral mucositis (Raber-Durlacher 2013).

Currently, evidence-based guidelines recommend growth factors for the prevention of oral mucositis in patients with haematological cancers undergoing high-dose chemotherapy and total body irradiation prior to haematopoietic stem cell transplantation (Lalla 2008). It has been postulated that tumour cells may also have receptors accommodating cytokines and growth factors, thus encouraging the proliferation of cancer cells in solid tumours (Lalla 2008; von Bültzingslöwen 2006). A 2010 systematic review suggested that the risk of acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) is increased in people with various cancers receiving chemotherapy with granulocyte colony-stimulating factor (G-CSF) when compared to those receiving chemotherapy without G-CSF (Lyman 2010). The authors concluded that it was not clear whether the increased AML/MDS risk was due to G-CSF or due to the increased chemotherapy dose-intensity in those patients. However, the review also reported a reduction in overall mortality for those receiving G-CSF.

Why it is important to do this review

This Cochrane Review is part of a series that will replace the previously published Cochrane Review covering all interventions for the prevention of oral mucositis in patients with cancer receiving treatment (Worthington 2011). The Mucositis Study Group (MSG) of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) is a group that was set up in 1998 for the purpose of producing international evidence-based clinical practice guidelines for managing mucositis (both oral and gastrointestinal), which they first published in 2004, with the latest update published in 2014 (Lalla 2014). In order to facilitate the future updating of Cochrane Reviews on this topic, and also to make them more usable to clinicians, guideline developers, and consumers, we have decided to divide the original Cochrane Review into the same intervention categories as those used by MASCC/ISOO, which are as follows:

- basic oral care/good clinical practice;
- growth factors and cytokines;
- anti-inflammatory agents;
- antimicrobials, mucosal coating agents, anaesthetics, and

analgesics;

- laser and other light therapy;
- cryotherapy;
- natural and miscellaneous agents;
- amifostine.

We believe that following the MASCC/ISOO structure will better enable the Cochrane Reviews to feed into such guidelines. We can also be more thorough and rigorous in our assessment and summarising of the evidence in each of the categories, which was not feasible in a single Cochrane Review approaching 150 included studies.

It is also important to do this review as it is consistently shown to be the most used review produced by Cochrane Oral Health (in terms of full-text downloads). It was also ranked by an expert panel of oral medicine specialists as being the most important topic in the field of oral medicine in an international prioritisation exercise carried out by Cochrane Oral Health in 2014 (Worthington 2015).

OBJECTIVES

To assess the effects of cytokines and growth factors for preventing oral mucositis in patients with cancer who are receiving treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) of parallel design. It is possible to conduct cross-over studies in this area as patients may receive several treatment sessions/cycles, with any mucositis completely healing in the periods between the sessions. However, we did not include cross-over data as we could not discount any period effects, with mucositis risk increasing as patients receive further cycles of treatment (Scully 2006; Sonis 2009). Instead, we used the first-period data only and treated such studies as parallel group studies.

Types of participants

We included all patients with cancer who were receiving treatment.

Types of interventions

We included studies comparing growth factors and cytokines for the prevention of oral mucositis (we would also have included targeted therapy-induced stomatitis had such studies been identified) against usual care, no treatment, or any other treatment to prevent oral mucositis. We also included studies comparing different growth factors and cytokines or different regimens of growth factors and cytokines against each other (head-to-head studies). We excluded studies with 'complex' interventions for the prevention of mucositis, such as lasers plus growth factors and cytokines versus lasers. This is because it is difficult to attribute any effect shown to any particular component of the intervention. We excluded studies assessing different cancer treatments where the primary outcome was survival/cure, with mucositis as a toxicity.

Types of outcome measures

We are in agreement with [Williamson 2012](#) that, if clinical trials and systematic reviews are to be utilised, the outcomes assessed should be those considered important to patients, healthcare professionals, and other key stakeholders. If outcomes and outcome measures are inconsistent across studies, it will not be possible to compare and summarise research, and there is potential for outcome reporting bias, with the selective reporting of results based on statistical significance and favourability ([Clarke 2007](#); [Dwan 2008](#); [Williamson 2005](#)). This can lead to exaggerated estimates of effect in systematic reviews of interventions, leading to an incorrect belief that an intervention is more beneficial than it truly is ([Clarke 2007](#)). It is thought that the way to address this problem is to develop disease- or condition-specific core outcome sets to be used as a minimum when conducting and reporting clinical trials ([Clarke 2007](#); [Williamson 2012](#)).

Therefore we used the core outcome set produced by [Bellm 2002](#), which is registered on the COMET (Core Outcome Measures in Effectiveness Trials) Initiative's website (www.comet-initiative.org), and is the only core outcome set for oral mucositis known to us. We added the outcomes 'interruptions to cancer treatment' and 'adverse events'.

Primary outcomes

Mucositis incidence of any severity. We used mucositis measured on a 0 to 4 point scale (none to severe) and dichotomised it as any mucositis (0 versus 1+), moderate to severe mucositis (0 to 1 versus 2+), and severe mucositis (0 to 2 versus 3+).

Some studies measure the effects of mucositis using a composite scale. If it was possible to extract the 'mucositis only' data from the total score, we would have included the data in the analyses. If it was not possible, we would have recorded the composite data in an additional table.

Secondary outcomes

- Interruptions to cancer treatment.
- Oral pain.
- Quality of life.
- Normalcy of diet (including use of percutaneous endoscopic gastrostomy (PEG) feeding tubes or total parenteral nutrition (TPN)).
- Adverse events.
- Number of days in hospital.
- Number of days of treatment with opioid analgesics.
- Number of days unable to take medicine orally.

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials without language or publication status restrictions:

- Cochrane Oral Health's Trials Register (searched 10 May 2017) ([Appendix 1](#));
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 4) in the Cochrane Library (searched 10 May 2017) ([Appendix 2](#));
- MEDLINE Ovid (1946 to 10 May 2017) ([Appendix 3](#));
- Embase Ovid (7 December 2015 to 10 May 2017) ([Appendix 4](#));
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 10 May 2017) ([Appendix 5](#));
- CANCERLIT (Cancer subset within PubMed; 1950 to 10 May 2017) ([Appendix 6](#)).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6 ([Lefebvre 2011](#)). Due to the Cochrane Embase Project to identify all clinical trials in the database and add them to CENTRAL, only most recent months of the Embase database were searched. See the [searching page on the Cochrane Oral Health website](#) for more information. No other restrictions were placed on the date of publication when searching the electronic databases.

Searching other resources

We searched the following trial registries for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 10 May 2017) ([Appendix 7](#));

- World Health Organization International Clinical Trials Registry Platform (apps.who.int/clinicaltrialssearch/; searched 10 May 2017) ([Appendix 8](#)).

We included only handsearching done as part of the Cochrane Worldwide Handsearching Programme and uploaded to CENTRAL.

We searched the reference lists of included studies and relevant systematic reviews for further studies.

We did not perform a separate search for adverse effects of interventions used, we considered adverse effects described in included studies only.

Data collection and analysis

Selection of studies

Two review authors independently screened the titles and abstracts retrieved from the electronic searches. We obtained full-text copies of all studies that appeared to meet the inclusion criteria of the review, or where there was insufficient information in the title or abstract to make a clear judgement. Two review authors independently assessed the full-text copies for eligibility and attempted to resolve any disagreements through discussion. We consulted a third review author when we were unable to resolve disagreements. On assessing the full-text article, we discarded any studies that clearly did not meet the inclusion criteria. We recorded all other studies that did not meet the inclusion criteria, along with reasons for exclusion, in the [Characteristics of excluded studies](#) table.

Data extraction and management

Two review authors independently extracted the data from each included study using a specially designed data extraction form, which we first piloted on a small sample of studies. We contacted study authors for clarification or missing data where necessary and feasible. We resolved any disagreements through discussion, consulting a third review author to achieve consensus when necessary. We recorded the following data for each included study in the [Characteristics of included studies](#) table.

- Trial design, location, number of centres, recruitment period.
- Inclusion/exclusion criteria, age and gender of participants, number randomised/analysed, any other potentially important prognostic factors (e.g. cancer type, cancer treatment, etc.).
- Detailed description of the intervention and comparator, including timing and duration. Information on compliance with the intervention.
- Details of the outcomes reported, including method of assessment and time(s) assessed.
- Details of sample size calculations, adverse effects, funding sources, declarations/conflicts of interest.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of each included study using the Cochrane domain-based, two-part tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We contacted study authors for clarification or missing information where necessary and feasible. We resolved any disagreements through discussion, consulting a third review author to achieve consensus when necessary. We completed a 'Risk of bias' table for each included study. For each domain of risk of bias, we first described what was reported to have happened in the study. This provided the rationale for our judgement of whether that domain was at low, high, or unclear risk of bias.

We assessed the following domains:

1. sequence generation (selection bias);
2. allocation concealment (selection bias);
3. blinding of participants and personnel (performance bias);
4. blinding of outcome assessment (detection bias);
5. incomplete outcome data (attrition bias);
6. selective outcome reporting (reporting bias);
7. other bias.

We categorised the overall risk of bias of individual studies. Studies were categorised as being at low, high, or unclear risk of bias according to the following criteria:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all domains were at low risk of bias;
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more domains were at high risk of bias; or
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more domains were at unclear risk of bias.

We also presented the 'Risk of bias' summary graphically.

Measures of treatment effect

For continuous outcomes (e.g. oral pain on a visual analogue scale) where studies used the same scale, we used the mean values and standard deviations (SDs) reported in the studies in order to express the estimate of effect as mean difference (MD) with 95% confidence interval (CI). Where different scales were used, we expressed the treatment effect as standardised mean difference (SMD) with 95% CI.

For dichotomous outcomes (e.g. mucositis of any severity/no mucositis), we expressed the estimate of effect as a risk ratio (RR) with 95% CI.

We did not use area under the curve (AUC) data due to variation in length of follow-up for outcome assessment, variation in the length of the scale used to measure the outcome and also variation or lack of clarity whether the results were reported in terms of total area under the curve or average over the time period.

Unit of analysis issues

The participant was the unit of analysis.

Dealing with missing data

We attempted to contact the author(s) of all included studies, where feasible, for clarification, and missing data. We would have used the methods described in Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* to estimate missing SDs (Higgins 2011). We did not use any other statistical methods or perform any further imputation to account for missing data.

Assessment of heterogeneity

When a sufficient number of studies were included in any meta-analyses, we assessed clinical heterogeneity by examining the characteristics of the studies, the similarity between the types of participants, the interventions, and the outcomes. We also assessed heterogeneity statistically using a χ^2 test, where a P value < 0.1 indicates statistically significant heterogeneity. We quantified heterogeneity using the I^2 statistic. A guide to interpretation of the I^2 statistic given in Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* is as follows (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

If at least 10 studies were included in a meta-analysis, we planned to assess publication bias according to the recommendations on testing for funnel plot asymmetry (Egger 1997), as described in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If asymmetry were identified, we would have examined possible causes. We were not able to assess publication bias in this way because, although we had a sufficient number of studies in our meta-analyses for the primary outcome in one comparison, they were split into subgroups containing less than 10 studies, with no pooling of the subgroup totals.

Data synthesis

We only carried out meta-analyses where there were studies of similar comparisons reporting the same outcomes. We combined MDs for continuous data, and RRs for dichotomous data. Our general approach was to use a random-effects model. With this approach, the CIs for the average intervention effect were wider than those that would have been obtained using a fixed-effect approach, leading to a more conservative interpretation. We used an additional table to report the results from studies not suitable for inclusion in a meta-analysis, but only for the primary outcome.

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses according to type of cancer treatment. We also would have considered age group (children versus adults) as a category for subgroup analyses, if there had been sufficient numbers of studies with these differing populations.

Sensitivity analysis

If there had been sufficient numbers of studies in the meta-analyses, we would have tested the robustness of our results by performing sensitivity analyses based on excluding the studies at unclear or high risk of bias from the analyses.

If any meta-analyses had included several small studies and a single very large study, we would have carried out a sensitivity analysis comparing the effect estimates from both random-effects and fixed-effect models. If these were different we would have reported on both analyses as part of the results section, and considered possible interpretation.

Presentation of main results

We produced a 'Summary of findings' table for each comparison in which there was more than one study in at least one of the subgroups based on cancer treatment. We included the incidence of moderate to severe oral mucositis, the incidence of severe oral mucositis and adverse events. We used GRADE methods (GRADE 2004), and the GRADEpro GDT online tool for developing 'Summary of findings' tables (www.guidelinedevelopment.org). We assessed the quality of the body of evidence for each comparison and outcome by considering the overall risk of bias of the included studies, the directness of the evidence, the inconsistency of the results, the precision of the estimates, and the risk of publication bias. We categorised the quality of each body of evidence as high, moderate, low, or very low.

RESULTS

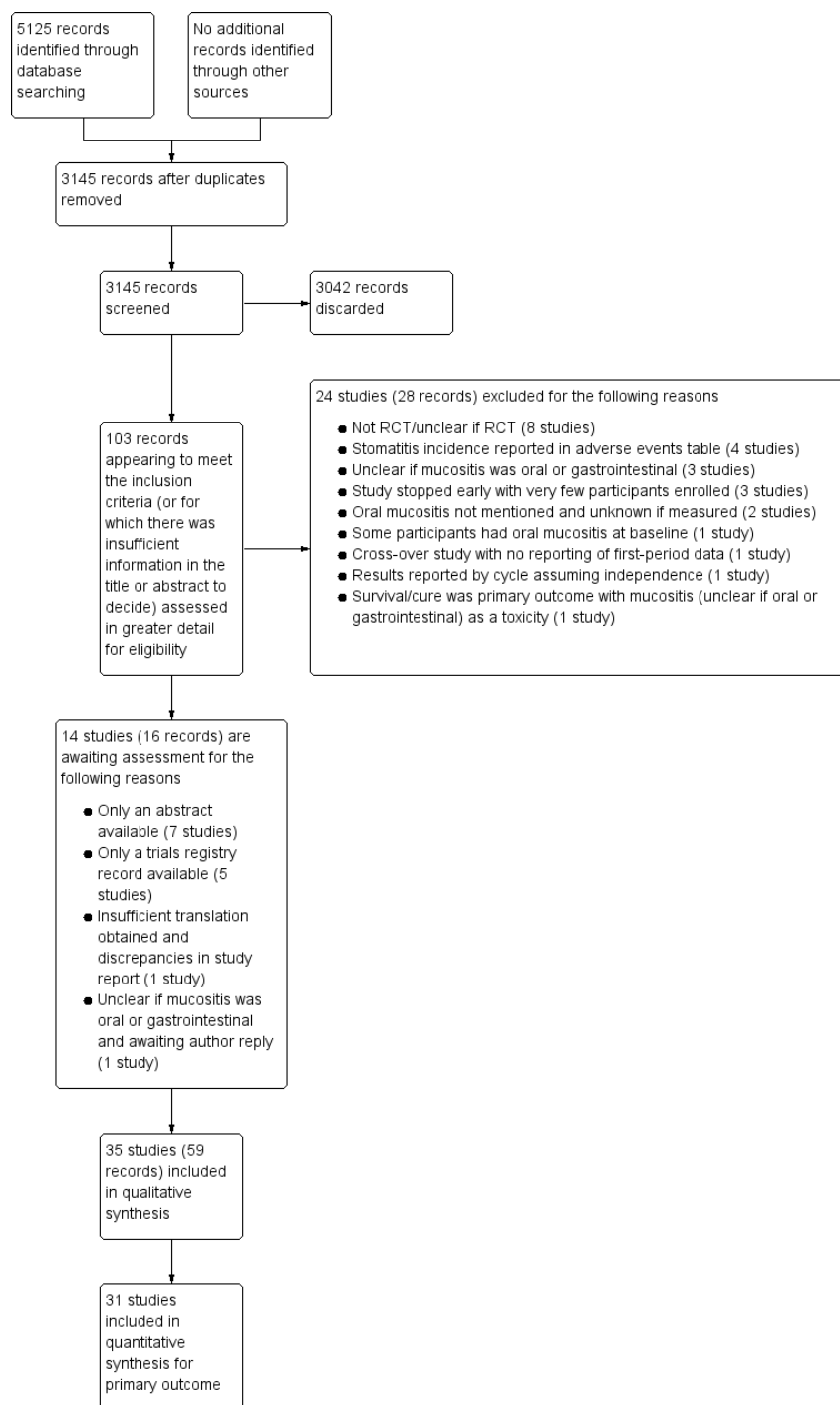
Description of studies

Results of the search

Our electronic searches identified 5125 records. After removing duplicates, this number was reduced to 3145. We examined the titles and abstracts of these records and discarded 3042, leaving 103 records to examine in more detail. Where possible, we obtained full-text copies of these potentially relevant records and linked any references pertaining to the same study under a single study ID. These 103 records represented 73 studies. We excluded 24 studies at this stage. The remaining 49 studies met our inclusion criteria

and we included 35 of these studies in the review. The remaining 14 studies are awaiting assessment because we do not have enough information to be able to include them in the review. We present this process as a study flow chart in [Figure 1](#).

Figure 1. Study flow diagram. RCT = randomised controlled trial.



Included studies

We included 35 studies in this review. For further information see the [Characteristics of included studies](#) tables.

Characteristics of the trials

Study design

One study was a cross-over design that reported the first-period data separately ([Chi 1995](#)), whilst the remaining studies all used a parallel design.

Number of arms

Twenty-seven studies had two arms, three studies had three arms ([Blijlevens 2013](#); [Freytes 2004](#); [Peterson 2009](#)), one study had four arms ([Wu 2009](#)), two studies had five arms ([Cartee 1995](#); [Linch 1993](#)), and two studies had seven arms ([Blazar 2006](#); [Meropol 2003](#)). Where studies had more than two arms, this was because they tested a range of doses of the cytokine/growth factor. In such instances we combined the arms testing different doses to make pairwise comparisons against the control group. Where possible, we also made head-to-head comparisons of doses ([Blijlevens 2013](#); [Cartee 1995](#); [Freytes 2004](#); [Meropol 2003](#); [Peterson 2009](#)).

Country

Nine studies were conducted in the USA ([Blazar 2006](#); [Cartee 1995](#); [Crawford 1999](#); [Freytes 2004](#); [Meropol 2003](#); [Schneider 1999](#); [Spielberger 2004](#); [Su 2006](#); [Vadhan-Raj 2010](#)), four in Italy ([Cesaro 2013](#); [Dazzi 2003](#); [Lucchese 2016a](#); [Lucchese 2016b](#)), two in each of South Korea ([Kim 2017](#); [Wu 2009](#)), the UK ([Linch 1993](#); [McAleese 2006](#)), Iran ([Gholizadeh 2016](#); [Hosseinjani 2017](#)), Finland ([Makkonen 2000](#); [Saarilahti 2002](#)), and one in each of the Netherlands ([van der Lelie 2001](#)), Russia ([Peterson 2009](#)), Japan ([Katano 1995](#)), Germany ([Fink 2011](#)), China ([Chi 1995](#)), Australia ([Bradstock 2014](#)), and France ([Antoun 2009](#)). The remaining seven studies were conducted across more than one country: USA and Australia ([Jagasia 2012](#); [Rosen 2006](#)); USA and Canada ([Nemunaitis 1995](#)); Australia, Canada and the USA ([Brizel 2008](#)); Australia, Canada and Europe ([Henke 2011](#)); Canada, USA and Europe ([Le 2011](#)); and 14 European countries ([Blijlevens 2013](#)).

Number of centres

Fifteen studies were conducted at a single-centre ([Antoun 2009](#); [Cartee 1995](#); [Chi 1995](#); [Dazzi 2003](#); [Fink 2011](#); [Hosseinjani 2017](#); [Katano 1995](#); [Kim 2017](#); [Lucchese 2016a](#); [Lucchese 2016b](#); [McAleese 2006](#); [Saarilahti 2002](#); [Su 2006](#); [Vadhan-Raj 2010](#); [van der Lelie 2001](#)). Eighteen studies were multicentric, ranging from two sites ([Blazar 2006](#); [Makkonen 2000](#)) to 46 sites ([Le 2011](#)). It was unclear how many centres were involved in the remaining two studies ([Gholizadeh 2016](#); [Schneider 1999](#)).

Trials registries

We were able to find a trials registry number for 13 studies ([Blijlevens 2013](#); [Bradstock 2014](#); [Cesaro 2013](#); [Fink 2011](#); [Gholizadeh 2016](#); [Henke 2011](#); [Hosseinjani 2017](#); [Jagasia 2012](#); [Kim 2017](#); [Le 2011](#); [McAleese 2006](#); [Spielberger 2004](#); [Vadhan-Raj 2010](#)), although only six studies mentioned it in the study report ([Bradstock 2014](#); [Cesaro 2013](#); [Gholizadeh 2016](#); [Hosseinjani 2017](#); [Kim 2017](#); [Vadhan-Raj 2010](#)), whilst a further study mentioned an obsolete number ([Jagasia 2012](#)).

Sample size calculation

Twenty-one studies reported details of sample size calculations, but four of these were not based on oral mucositis ([Cesaro 2013](#); [Crawford 1999](#); [Jagasia 2012](#); [Su 2006](#)). One further study stated that 36 participants “should be enough to demonstrate a clinically significant difference”, with no details reported ([van der Lelie 2001](#)).

Funding and conflicts of interest

This information is difficult to summarise as it was not always adequately reported.

Nineteen studies appeared to be funded by industry alone i.e. it was explicitly stated that they received industry funding or that industry supplied the interventions or both. Five studies appeared to be funded by government/public sector alone and did not state whether or not the interventions were supplied by industry ([Cartee 1995](#); [Lucchese 2016a](#); [Lucchese 2016b](#); [Su 2006](#); [Wu 2009](#)). Four studies reported both government and industry funding, three of which stated that industry provided the interventions ([Bradstock 2014](#); [Chi 1995](#); [Kim 2017](#)), and one of which was not clear ([Blazar 2006](#)). Two studies stated that there was no funding for the study ([Cesaro 2013](#); [Hosseinjani 2017](#)). The remaining five studies did not mention funding ([Dazzi 2003](#); [Freytes 2004](#); [Gholizadeh 2016](#); [McAleese 2006](#); [Saarilahti 2002](#)).

Ten studies, all industry funded, declared conflicts of interest for reasons such as board membership of the funder, employment or

leadership roles with the funder, receipt of lecture fees or consultancy fees or research funding or honoraria from the funder (Antoun 2009; Blijlevens 2013; Brizel 2008; Henke 2011; Jagasia 2012; Le 2011; Peterson 2009; Rosen 2006; Spielberger 2004; Vadhan-Raj 2010). Six of those studies also declared that some authors owned equity/stock with the funder (Brizel 2008; Henke 2011; Jagasia 2012; Le 2011; Rosen 2006; Spielberger 2004). Three studies did not explicitly declare conflicts of interest, but some authors were employed by the funder (Crawford 1999; Linch 1993; Nemunaitis 1995). Eight studies stated that there were no conflicts of interest (Bradstock 2014; Cesaro 2013; Gholizadeh 2016; Hosseinjani 2017; Kim 2017; Lucchese 2016a; Lucchese 2016b; Su 2006). The remaining 14 studies did not mention conflicts of interest.

Characteristics of the participants

Number randomised/analysed

The studies randomised 3218 participants, of whom 3102 were included in the studies' analyses (the latter number does not include any participants from Makkonen 2000, as this study did not report how many of the 40 randomised participants were analysed).

Age and sex

The age of the participants ranged from 1 to 87 years, with four studies only including children and young adults (i.e. up to 18 years) (Cesaro 2013; Gholizadeh 2016; Lucchese 2016a; Lucchese 2016b). Of the 31 studies including adult participants, one had a median age of 29 (Dazzi 2003), two had mean or median ages in their 30s (Linch 1993; Nemunaitis 1995), nine in their 40s (Blazar 2006; Bradstock 2014; Cartee 1995; Chi 1995; Hosseinjani 2017; Jagasia 2012; Spielberger 2004; Vadhan-Raj 2010; van der Lelie 2001), 11 in their 50s (Blijlevens 2013; Brizel 2008; Fink 2011; Freytes 2004; Henke 2011; Katano 1995; Kim 2017; Le 2011; Peterson 2009; Saarilahti 2002; Wu 2009), seven in their 60s (Antoun 2009; Crawford 1999; Makkonen 2000; McAleese 2006; Meropol 2003; Rosen 2006; Su 2006), and one study did not report the age, although the inclusion criteria stated that they must be at least 18 years old (Schneider 1999). In 24 studies, there was a clear majority of male participants, whilst the male to female ratio was roughly equal in seven studies. In three studies there were more female participants, although two of these exclusively included breast cancer patients (Cartee 1995; Katano 1995), whilst the third included colorectal cancer patients (Peterson 2009).

Cancer type

Fourteen studies enrolled participants with haematological cancers (Blazar 2006; Blijlevens 2013; Bradstock 2014; Fink 2011;

Freytes 2004; Gholizadeh 2016; Hosseinjani 2017; Jagasia 2012; Kim 2017; Lucchese 2016a; Lucchese 2016b; Nemunaitis 1995; Spielberger 2004; van der Lelie 2001). Eighteen studies enrolled participants with solid cancers: head and neck (Brizel 2008; Chi 1995; Henke 2011; Le 2011; Makkonen 2000; McAleese 2006; Saarilahti 2002; Schneider 1999; Su 2006; Wu 2009); colorectal (Antoun 2009; Meropol 2003; Peterson 2009; Rosen 2006); breast (Cartee 1995; Katano 1995); lung (Crawford 1999); and sarcoma (Vadhan-Raj 2010). The remaining three studies enrolled a mixture of participants with solid cancers and participants with haematological cancers, two of which were 80% to 90% solid (Cesaro 2013; Dazzi 2003), and the other study only 3% solid (Linch 1993).

Cancer treatment

In 11 studies, the participants received chemotherapy only (Antoun 2009; Bradstock 2014; Cartee 1995; Chi 1995; Crawford 1999; Gholizadeh 2016; Katano 1995; Meropol 2003; Peterson 2009; Rosen 2006; Vadhan-Raj 2010). Of the 15 studies in which the participants received conditioning therapy prior to stem cell or bone marrow transplantation, five of these involved chemotherapy only (Blijlevens 2013; Dazzi 2003; Fink 2011; Hosseinjani 2017; Kim 2017), and one involved total body irradiation (TBI) only (Lucchese 2016b). In the remaining nine transplant studies, all the participants had chemotherapy, but the proportion of participants also receiving TBI differed: 100% (Lucchese 2016a; Nemunaitis 1995; Spielberger 2004); around 50% (Blazar 2006; Jagasia 2012; van der Lelie 2001); 29% (Linch 1993); 10% or less (Cesaro 2013; Freytes 2004). The remaining nine studies were all on head and neck cancer patients where the participants either had radiotherapy to the head and neck alone (Makkonen 2000; McAleese 2006; Saarilahti 2002; Schneider 1999; Su 2006), or radiotherapy to the head and neck plus chemotherapy (Brizel 2008; Henke 2011; Le 2011; Wu 2009), although in one of those studies only 50% of participants had the chemotherapy (Wu 2009).

Of the 15 transplant studies, four involved allogeneic transplants (Blazar 2006; Jagasia 2012; Lucchese 2016b; Nemunaitis 1995), nine involved autologous transplants (Blijlevens 2013; Cesaro 2013; Dazzi 2003; Fink 2011; Freytes 2004; Hosseinjani 2017; Kim 2017; Lucchese 2016a; Spielberger 2004), with the remaining two involving a mixture (Linch 1993; van der Lelie 2001).

In six studies, all participants received granulocyte-colony stimulating factor (a growth factor) as part of the cancer treatment to prevent neutropenia. Four of these studies were investigating keratinocyte growth factor (Blazar 2006; Bradstock 2014; Spielberger 2004; Vadhan-Raj 2010), and two were investigating granulocyte-macrophage colony-stimulating factor (Cartee 1995; Dazzi 2003). Giving all participants this growth factor would have the potential to lessen the impact of the study intervention.

Characteristics of the interventions and comparisons

Keratinocyte growth factor (KGF)

Of the 16 studies investigating KGF, one study assessed KGF-2 (repifermin) (Freytes 2004), whilst the remaining studies assessed KGF-1 (palifermin).

Fourteen studies used a placebo comparator (Blazar 2006; Blijlevens 2013; Bradstock 2014; Brizel 2008; Freytes 2004; Henke 2011; Jagasia 2012; Le 2011; Lucchese 2016a; Lucchese 2016b; Meropol 2003; Rosen 2006; Spielberger 2004; Vadhan-Raj 2010), one was KGF plus standard care versus standard care alone (Fink 2011), and the remaining study used a chlorhexidine mouthwash comparator (Gholizadeh 2016).

In all studies, KGF was given intravenously. The most common total dosage received was 360 µg/kg in seven studies (Bradstock 2014; Fink 2011; Gholizadeh 2016; Jagasia 2012; Lucchese 2016a; Lucchese 2016b; Spielberger 2004). The dosage varied greatly in the other studies: 120 µg/kg (Rosen 2006); 180 µg/kg (Vadhan-Raj 2010); 600 µg/kg (Brizel 2008); 840 µg/kg to 960 µg/kg depending on resection type (Henke 2011); 1440 µg/kg (Le 2011). The dosages varied within the remaining studies due to multiple arms receiving different doses: 3 µg/kg to 240 µg/kg (Meropol 2003); 180 µg/kg to 360 µg/kg (Blijlevens 2013); 240 µg/kg to 720 µg/kg (Blazar 2006); 325 µg/kg to 650 µg/kg (Freytes 2004).

The number of doses received ranged from one (Vadhan-Raj 2010) to 13 (Freytes 2004), but the most common was six (Blijlevens 2013; Bradstock 2014; Fink 2011; Gholizadeh 2016; Lucchese 2016a; Lucchese 2016b; Spielberger 2004).

Reporting of compliance varied too greatly to summarise succinctly but compliance was generally high (see Characteristics of included studies).

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

Of the eight studies investigating GM-CSF, four used a placebo comparator (Cartee 1995; Dazzi 2003; Nemunaitis 1995; van der Lelie 2001), two used a no-treatment comparator (Chi 1995; McAleese 2006), one was GM-CSF plus sucralfate versus sucralfate alone (Makkonen 2000), and the remaining study used a sucralfate comparator (Saarilahti 2002).

In three studies, GM-CSF was given by subcutaneous injection (Chi 1995; Makkonen 2000; McAleese 2006). In Makkonen 2000, both arms received sucralfate mouthwash that was swallowed after rinsing. In three studies, GM-CSF was taken as a mouthwash (Cartee 1995; Dazzi 2003; Saarilahti 2002). In Saarilahti 2002, both the GM-CSF and sucralfate comparator mouthwashes were swallowed after rinsing. In one study, GM-CSF was given as an oral gel and swallowed after holding in the mouth (van der Lelie 2001). In the remaining study, GM-CSF was given intravenously (Nemunaitis 1995).

Total dosage varied greatly: 40 µg (Chi 1995); 2100 µg (McAleese 2006); 5250 µg/m² (Nemunaitis 1995). The dosages ranged from 12.6 µg to 12,600 µg within one study due to multiple arms receiving different doses (Cartee 1995). Another study reported a mean total dosage of 3398 µg, but this total ranged from 300 µg to 7200 µg depending on the participant's weight and the length of radiotherapy course (Makkonen 2000). In two studies, the dose was 150 µg per day but the total received varied depending on neutrophil recovery (Dazzi 2003), and the length of radiotherapy course (Saarilahti 2002). In the remaining study, the dose was 300 µg per day but the total received varied depending on neutrophil recovery (van der Lelie 2001).

As is obvious from the variation in total dosage, the number of doses received varied greatly both between studies and within studies. Compliance was also reported inconsistently but was generally high (see Characteristics of included studies).

Granulocyte-colony stimulating factor (G-CSF)

Of the six studies investigating G-CSF, four used a placebo comparator (Crawford 1999; Linch 1993; Schneider 1999; Su 2006), one used a no-treatment comparator (Katano 1995), and the remaining study compared a type of G-CSF that is given as a single dose (pegfilgrastim) with the standard G-CSF that is given in multiple doses (filgrastim) (Cesaro 2013).

Four studies reported that G-CSF was given by subcutaneous injection (Crawford 1999; Katano 1995; Schneider 1999; Su 2006), whilst one did not specify, but was probably subcutaneous (Cesaro 2013), and the remaining study was intravenous delivery (Linch 1993).

Total dosage varied: 3220 µg/m² (Crawford 1999); 3 µg/kg per day with the total dependent on neutrophil counts and the length of radiotherapy course (Schneider 1999; Su 2006); 2 µg/kg to 15 µg/kg per day due to multiple arms receiving different dosages with the total was depending on neutrophil recovery (Linch 1993); 125 µg per day with total depending on neutrophil recovery (Katano 1995); 100 µg/kg in the pegfilgrastim arm and at least 45 µg/kg in the filgrastim arm (Cesaro 2013).

The number of doses received varied both between studies and within studies. Compliance was reported as being 100% in one study (Cesaro 2013), whilst one study only reported that the interventions were well tolerated (Schneider 1999), and the remaining four studies did not report on compliance.

Epidermal growth factor (EGF)

Two studies investigated an oral spray of EGF, both using a placebo comparator (Kim 2017; Wu 2009). Total dosage was unclear in both studies but the daily dose was 50 µg/mL (six sprays twice daily) in one study (Kim 2017), and 10 µg to 100 µg per day (due to multiple arms receiving different dosages) in the other study (Wu 2009). The number of doses varied depending on neutrophil

recovery and resolution of oral mucositis in [Kim 2017](#), whilst participants in [Wu 2009](#) received the interventions daily for five weeks but it was not clear if that meant only on the radiotherapy days (five days per week) or seven days per week. Compliance was reported as a median of 93% and 92% in the EGF and placebo groups respectively in [Kim 2017](#), but compliance was not reported in [Wu 2009](#).

Intestinal trefoil factor (ITF)

One study investigated an oral spray of ITF using a placebo comparator ([Peterson 2009](#)). The ITF was not expectorated. The study included two ITF arms with total dosages of 336 mg and 2688 mg. The mode of administration was three sprays to the oral mucosa eight times daily for 14 days. Patient-reported compliance was 97%.

Erythropoietin

One study investigated a mouthwash of erythropoietin using a placebo comparator ([Hosseini 2017](#)). Neither swallowing nor expectoration was reported. The mouthwash was taken as 15 mL (50 IU/mL) four times daily (daily dosage of 3000 IU) for 14 days or until neutrophil recovery, whichever occurred first. Compliance was reported narratively as being low but no reason was stated.

Transforming growth factor (TGF)

One study investigated TGF-beta(2) using a placebo comparator ([Antoun 2009](#)). The dosage was 2 ng of TGF per mg protein mixed with cool boiled water at 0.23 g/mL (100 kcal/100 mL). During each cycle participants received 750 mL to 1000 mL per day plus any other food desired. The formula was administered for two days before, two days during, and three days after chemotherapy (seven days/cycle), for one to eight cycles. Compliance was poor i.e. nine participants did not eat the formula and were excluded.

Characteristics of the outcomes

Primary outcome

For the primary outcome of oral mucositis, we were interested in both the presence/absence of oral mucositis, and also different levels of severity. All 35 studies assessed and reported the incidence of oral mucositis. Twenty-two studies primarily used the WHO (World Health Organization) 0 to 4 scale, whilst four used the NCI-CTC (National Cancer Institute common toxicity criteria) 0 to 4 scale ([Brizel 2008](#); [Dazzi 2003](#); [Freytes 2004](#); [Kim 2017](#)), four used the RTOG (Radiation Therapy Oncology Group) 0 to 4 scale ([Chi 1995](#); [McAleese 2006](#); [Saarilahti 2002](#); [Wu 2009](#)), one used the CALGB (Cancer and Leukemia Group B) 0 to 4 scale ([Cartee 1995](#)), one used an unnamed 0 to 2 scale ([Makkinen](#)

[2000](#)), one used an unnamed 0 to 3 scale ([Su 2006](#)), one used an unnamed 0 to 4 scale ([Nemunaitis 1995](#)), and the remaining study did not mention a scale and only reported the incidence of stomatitis ([Linch 1993](#)). The different oral mucositis assessment scales are described in [Appendix 9](#).

Twelve studies reported the data in our preferred format which was the maximum oral mucositis score experienced by each participant over the length of the study, allowing us to dichotomise the data into various levels of severity as described in the section [Primary outcomes](#). Eighteen studies reported a particular level of severity (e.g. grade 3 or above). One study reported the incidence of each oral mucositis grade on multiple assessment days. We were unable to use the data from the remaining four studies for analysis due to unclear or lack of reporting ([Linch 1993](#); [Lucchese 2016a](#); [Lucchese 2016b](#); [Makkinen 2000](#)).

The frequency of oral mucositis assessment and the duration for which it was assessed varied greatly across the studies, often depending on whether the participants received radiotherapy, and often depending on the speed of neutrophil recovery, resolution of oral mucositis, or duration of hospitalisation. Four studies did not report the frequency of assessment ([Antoun 2009](#); [Cesaro 2013](#); [Linch 1993](#); [Nemunaitis 1995](#)), whilst a further study was unclearly reported ([Lucchese 2016b](#)). Twelve studies reported daily assessments, eight reported weekly assessments, with the remainder falling somewhere in between these two frequencies. Where participants had multiple cycles of treatment, we only reported the results for the first cycle if these data were available separately.

Secondary outcomes

Interruptions to cancer treatment

Six studies reported data that we were able to use in analyses ([Brizel 2008](#); [Henke 2011](#); [Le 2011](#); [Saarilahti 2002](#); [Su 2006](#); [Wu 2009](#)), whilst a further two studies assessed this outcome but either did not report the interruption by treatment arm ([Makkinen 2000](#)), or narratively reported that there were no differences, with no numerical data ([Schneider 1999](#)).

Two studies reported this outcome as the incidence of unscheduled radiotherapy breaks of five or more days ([Brizel 2008](#); [Henke 2011](#); [Le 2011](#)). Two of those studies also reported on chemotherapy delays/discontinuations ([Henke 2011](#); [Le 2011](#)). The remaining studies all reported on the incidence of interruptions to radiotherapy treatment, one of which stated that interruptions were specifically due to oral mucositis ([Saarilahti 2002](#)), and another reporting the incidence of three or more consecutive days of interruption ([Wu 2009](#)).

Oral pain

Four studies reported data that we were able to use in analyses (Dazzi 2003; Freytes 2004; Henke 2011; Le 2011). Two of these studies used a 0 to 4 scale and reported the mean (Henke 2011; Le 2011), whilst the other two studies used a 0 to 10 scale and reported the mean worst score experienced (Dazzi 2003; Freytes 2004).

Of the 11 other studies that reported that oral pain was an outcome of the study, five reported the results as area under the curve (AUC) but, for reasons stated in the section [Measures of treatment effect](#), we did not meta-analyse these data (Blijlevens 2013; Kim 2017; Lucchese 2016a; Rosen 2006; Spielberger 2004). Two studies reported medians, which are not suitable for meta-analysis (Vadhan-Raj 2010; van der Lelie 2001). One study reported the data graphically as a mean over time with no standard deviation (Saarilahti 2002). One study narratively reported that there were no differences, with no numerical data (Wu 2009). The remaining two studies used two different scales: one reported as “no difference” and another reported on a graph with no standard deviation (Makkonen 2000); both reported on a graph over time, with one also reported as AUC (Meropol 2003).

Quality of life

Four studies assessed quality of life using various assessment scales: European Quality Of Life Utility Scale - EQ-5D (Blijlevens 2013); modified Oral Mucositis Daily Questionnaire - OMDQ (Kim 2017); Functional Assessment of Cancer Therapy - FACT (Spielberger 2004); an unnamed 1 to 7 scale (Vadhan-Raj 2010). We did not use the data in our analyses as they were either reported as AUC (Kim 2017; Spielberger 2004), as a median (Vadhan-Raj 2010), or the mean was reported at one very early time point with no standard deviation (Blijlevens 2013).

Normalcy of diet - including use of percutaneous endoscopic gastrostomy (PEG) feeding tubes or total parenteral nutrition (TPN)

Fourteen studies reported data that we were able to use in analyses in the form of: incidence of TPN (Blijlevens 2013; Cesaro 2013; Fink 2011; Jagasia 2012; Kim 2017; Spielberger 2004; van der Lelie 2001); incidence of PEG (Brizel 2008; Saarilahti 2002; Su 2006); incidence of TPN, PEG, nasogastric tube or intravenous (IV) hydration (Henke 2011; Le 2011); incidence of “tube feeding” (McAleese 2006); ability to eat using a 1 to 4 scale (Freytes 2004). Only one of these studies explicitly stated that supplemental feeding was due to oral mucositis (Henke 2011).

Two further studies only reported the duration of TPN (Lucchese 2016a; Lucchese 2016b), and another study used 0 to 4 scales to assess difficulty in eating and drinking, but reported median scores (Vadhan-Raj 2010).

We combined studies reporting incidence of TPN, PEG, etc., in meta-analyses of ‘supplemental feeding’.

Adverse events

This outcome was very poorly reported with some studies reporting numerical data and some reporting narratively. Some studies only reported adverse events if there was a minimum incidence (which varied between studies) or if there was a specified difference in incidence between treatment arms. It was also difficult to determine whether or not many adverse effects were due to the study interventions, or due to the underlying cancer treatment. We presented adverse event data/information only in an additional table.

Number of days in hospital

Two studies reported data that we were able to use in analyses i.e. mean and standard deviations (Blijlevens 2013; Hosseinjani 2017).

Five further studies reported medians (Cesaro 2013; Fink 2011; Linch 1993; Nemunaitis 1995; van der Lelie 2001). One study reported data graphically with no standard deviation or P value (Crawford 1999). One study listed this as an outcome of the study but did not actually report it (Kim 2017). One study reported the incidence of hospitalisation (Saarilahti 2002).

Number of days of treatment with opioid analgesics

Two studies reported data that we were able to use in analyses i.e. mean and standard deviations (Blijlevens 2013; Dazzi 2003; Freytes 2004). Only one study specified that the opioid use was due to oral mucositis (Freytes 2004).

Four further studies reported medians (Fink 2011; Kim 2017; Lucchese 2016a; Spielberger 2004), whilst another study did not state whether the data were means or medians, and there were no standard deviations or P value (Lucchese 2016b). Three studies reported total dose of opioid analgesic (Henke 2011; Le 2011; Vadhan-Raj 2010), whilst four studies reported the incidence of its use (Hosseinjani 2017; Jagasia 2012; Saarilahti 2002; van der Lelie 2001). One study stated that it assessed the use of opioid analgesics, but did not specify whether this was in terms of duration, quantity or incidence, and did not actually report any data (Wu 2009).

Number of days unable to take medicine orally

No studies reported this outcome.

Excluded studies

We excluded 24 studies from this review for the following reasons.

- Not a randomised controlled trial or unclear (Foncuberta 2001; Gordon 1993; Horsley 2007; Hunter 2009; Iwase 1997; Limaye 2013; Throuvalas 1995; Vitale 2014).
- Stomatitis incidence reported in adverse events table (Kubo 2016; Lee 2016; Nabholz 2002; Tsurusawa 2016).
- Unclear if mucositis was oral or gastrointestinal (Jones 1996; Legros 1997; Pettengell 1992).
- Study stopped early with very few participants enrolled (Antin 2002; NCT00360971; NCT00626639).
- Oral mucositis not mentioned and unknown if measured (Gebbia 1994; Gladkov 2013).
- Some participants had oral mucositis at baseline (Ryu 2007).
- Cross-over study with no reporting of first-period data (de Koning 2007).
- Results reported by cycle assuming independence (Karthaus 1998).
- Survival/cure was primary outcome with mucositis (unclear if oral or gastrointestinal) as a toxicity (Ifrah 1999).

Risk of bias in included studies

Allocation

Random sequence generation

Nineteen studies described an adequate method of generating a random sequence, so we assessed these as at low risk of bias. The remaining 16 studies stated that they were randomised without providing a description of how the random sequence was generated, so we assessed these as at unclear risk of bias.

Allocation concealment

Seventeen studies described a process that would have concealed the random sequence from those involved in the study, thus allowing it to be applied as it was generated. We assessed these 17 studies as at low risk of bias. The remaining 18 studies did not describe any methods used to conceal the random sequence, so we assessed them as at unclear risk of bias.

In total, 16 studies are at low risk of selection bias, meaning that we assessed both of the above domains as low risk of bias. The remaining 19 studies are at unclear risk of selection bias because one or both of the above domains were rated as unclear.

Most studies were carried out in middle-income and high-income countries with strict controls and regulations and we feel that many of them probably had adequate randomisation, and that the unclear ratings for these two domains were probably due to reporting issues rather than actual bias. Therefore, when incorporating risk

of bias into our GRADE assessments, we did not downgrade any evidence based on selection bias.

Blinding

Blinding of participants and personnel (performance bias)

We assessed 28 studies as at low risk of bias. Twenty-seven of these studies used a placebo comparator and this ensured that blinding was performed successfully. One further study compared GM-CSF with sucralfate, but the interventions were supplied as identical-looking mouthwashes, the study was described as double-blind, and there was no reason to suspect that participants or personnel were not blinded (Saarilahti 2002).

We assessed seven studies as at high risk of bias. Three of these studies used a no-treatment comparator, so blinding was not possible (Chi 1995; Katano 1995; McAleese 2006). Two other studies were similar in that they compared KGF plus best supportive care with best supportive care alone (Fink 2011), and GM-CSF plus sucralfate with sucralfate alone (Makkonen 2000). One study compared intravenous KGF with a chlorhexidine mouthwash (Gholizadeh 2016). The remaining study compared two types of G-CSF, but the dosing schedule was very different, ensuring that blinding was not possible (Cesaro 2013).

Blinding of outcome assessment (detection bias)

We assessed 29 studies as at low risk of bias. We assessed four studies as at unclear risk of bias because blinding of outcome assessment was not mentioned, but we judged that it would have been possible to achieve (Cesaro 2013; Chi 1995; Katano 1995; Makkonen 2000). We assessed the remaining two studies as at high risk of bias because they either stated that there was no blinding of outcome assessors (Fink 2011), or it was implied by the description "single-blind" (Linch 1993).

Incomplete outcome data

Attrition was generally very low and we assessed 31 studies as at low risk of bias. We assessed two studies as at unclear risk of bias because one did not report how many of the randomised participants were included in the analyses (Makkonen 2000), and the other did not report the attrition by treatment arm but there was potential for bias if the dropouts were mostly from one arm and had developed the outcome of severe oral mucositis (Cartee 1995). We assessed two studies as at high risk of bias because one had very high attrition (Antoun 2009), and the other had 19% attrition in one arm compared to none in the other arm (Fink 2011).

Selective reporting

It is important to note that we have perhaps been quite lenient when rating bias under this domain. We have tended to focus on the primary outcome because the vast majority of the data are for this outcome. Many studies have only reported a particular level of oral mucositis severity, for example grade 2 to 4 (ulcerative/moderate to severe), when they could have reported more usable data by reporting the maximum grade experienced per patient, allowing us to dichotomise this into all severities. Some readers may consider this to be bias but we have reported all this information transparently in the [Characteristics of included studies](#) tables, thus allowing the reader to decide if they would judge the risk of bias differently. Furthermore, many secondary outcomes were reported poorly or in a way that was not amenable to meta-analysis, which in most cases is a reporting issue rather than a bias issue. This highlighted the problem with the current Cochrane risk of bias tool in that meta-analyses are being biased due to missing information, but this is not being accounted for in the meta-analysis. It does not seem appropriate to rate a study at high risk of bias due to a secondary outcome when it is contributing data to the meta-analysis for the primary outcome, and it is the meta-analysis for the secondary outcome that is affected by bias. Again, all this information is clearly reported in the [Characteristics of included studies](#) tables.

We assessed 32 studies as at low risk of bias. We assessed the remaining three studies as at high risk of bias, two because there were

no usable data for the primary outcome ([Linch 1993](#); [Makkonen 2000](#)), and one because several outcomes were assessed but not reported ([Wu 2009](#)).

Other potential sources of bias

We did not consider there to be any issues arising from other potential sources of bias in any of the studies and we therefore assessed them all as at low risk of other bias.

Overall risk of bias

- Thirteen studies (37%) were at low overall risk of bias ([Blijlevens 2013](#); [Dazzi 2003](#); [Freytes 2004](#); [Henke 2011](#); [Hosseinjani 2017](#); [Kim 2017](#); [Le 2011](#); [Lucchese 2016a](#); [Lucchese 2016b](#); [Saarilahti 2002](#); [Schneider 1999](#); [Su 2006](#); [Vadhan-Raj 2010](#)).
- Twelve studies (34%) were at unclear overall risk of bias ([Blazar 2006](#); [Bradstock 2014](#); [Brizel 2008](#); [Cartee 1995](#); [Crawford 1999](#); [Jagasia 2012](#); [Meropol 2003](#); [Nemunaitis 1995](#); [Peterson 2009](#); [Rosen 2006](#); [Spielberger 2004](#); [van der Lelie 2001](#)).
- Ten studies (29%) were at high overall risk of bias ([Antoun 2009](#); [Cesaro 2013](#); [Chi 1995](#); [Fink 2011](#); [Gholizadeh 2016](#); [Katano 1995](#); [Linch 1993](#); [Makkonen 2000](#); [McAleese 2006](#); [Wu 2009](#)).

Risk of bias can be viewed graphically in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Antoun 2009	?	?	+	+	+	+	+
Blazar 2006	?	?	+	+	+	+	+
Blijlevens 2013	+	+	+	+	+	+	+
Bradstock 2014	+	?	+	+	+	+	+
Brizel 2008	?	?	+	+	+	+	+
Cartee 1995	+	+	+	+	?	+	+
Cesaro 2013	+	+	+	?	+	+	+
Chi 1995	?	?	+	?	+	+	+
Crawford 1999	?	?	+	+	+	+	+
Dazzi 2003	+	+	+	+	+	+	+
Fink 2011	?	?	+	+	+	+	+
Freytes 2004	+	+	+	+	+	+	+
Gholizadeh 2016	+	?	+	+	+	+	+
Henke 2011	+	+	+	+	+	+	+
Hosseiniyani 2017	+	+	+	+	+	+	+
Jagasia 2012	?	?	+	+	+	+	+
Katano 1995	?	?	+	?	+	+	+
Klim 2017	+	+	+	+	+	+	+
Le 2011	+	+	+	+	+	+	+
Linch 1993	+	?	+	+	+	+	+
Lucchese 2016a	+	+	+	+	+	+	+
Lucchese 2016b	+	+	+	+	+	+	+
Makkonen 2000	+	+	+	?	?	+	+
McAleese 2006	?	?	+	+	+	+	+
Meropol 2003	?	?	+	+	+	+	+
Nemunaitis 1995	?	+	+	+	+	+	+
Peterson 2009	?	?	+	+	+	+	+
Rosen 2006	?	?	+	+	+	+	+
Saarialhti 2002	+	+	+	+	+	+	+
Schneider 1999	+	+	+	+	+	+	+
Spielberger 2004	?	?	+	+	+	+	+
Su 2006	+	+	+	+	+	+	+
Vadhan-Raj 2010	+	+	+	+	+	+	+
van der Lelie 2001	?	?	+	+	+	+	+
Wu 2009	?	?	+	+	+	+	+

Effects of interventions

See: [Summary of findings for the main comparison](#) Keratinocyte growth factor (KGF) compared to placebo for preventing oral mucositis in adults with cancer receiving treatment; [Summary of findings 2](#) Granulocyte-macrophage colony-stimulating factor (GM-CSF) compared to placebo/no treatment for preventing oral mucositis in adults with cancer receiving treatment; [Summary of findings 3](#) Granulocyte-colony stimulating factor (G-CSF) compared to placebo/no treatment for preventing oral mucositis in adults with cancer receiving treatment. We used GRADE methods to assess the quality of the body of evidence for each comparison in which there was more than one study in at least one of the subgroups based on cancer treatment. We included the incidence of moderate to severe oral mucositis, the incidence of severe oral mucositis and adverse events. These assessments are presented in [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#).

Keratinocyte growth factor (KGF) versus placebo

Oral mucositis

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

There was insufficient evidence from four studies, one at low ([Blijlevens 2013](#)), two at unclear ([Blazar 2006](#); [Spielberger 2004](#)), and one at high risk of bias ([Fink 2011](#)), to determine whether or not KGF reduces the risk of any level of oral mucositis: risk ratio (RR) 0.96, 95% confidence interval (CI) 0.88 to 1.05; 655 participants ([Analysis 1.1](#)).

Six studies, two at low ([Blijlevens 2013](#); [Freytes 2004](#)), three at unclear ([Blazar 2006](#); [Jagasia 2012](#); [Spielberger 2004](#)), and one at high risk of bias ([Fink 2011](#)), showed a reduction in the risk of moderate to severe oral mucositis in favour of KGF: RR 0.89, 95% CI 0.80 to 0.99; 852 participants ([Analysis 1.2](#)).

The same six studies showed a possible reduction in the risk of severe oral mucositis in favour of KGF, but there is also some possibility of an increase in risk: RR 0.85, 95% CI 0.65 to 1.11; 852 participants ([Analysis 1.3](#)).

Heterogeneity present in these meta-analyses may partly be due to differences between studies where transplants were autologous or allogeneic.

Adults receiving radiotherapy to the head and neck with cisplatin/fluorouracil (5FU)

Two studies, both at low risk of bias ([Henke 2011](#); [Le 2011](#)), showed a reduction in the risk of any level of oral mucositis in favour of KGF: RR 0.95, 95% CI 0.90 to 1.00; $P = 0.04$; 374 participants ([Analysis 1.1](#)).

Three studies, two at low ([Henke 2011](#); [Le 2011](#)), and one at unclear risk of bias ([Brizel 2008](#)), showed a reduction in the risk of moderate to severe oral mucositis in favour of KGF: RR 0.91, 95% CI 0.83 to 1.00; $P = 0.04$; 471 participants ([Analysis 1.2](#)).

The same three studies showed a reduction in the risk of severe oral mucositis in favour of KGF: RR 0.79, 95% CI 0.69 to 0.90; 471 participants ([Analysis 1.3](#)).

Adults receiving chemotherapy alone for mixed cancers

Two studies, both at unclear risk of bias ([Bradstock 2014](#); [Rosen 2006](#)), showed a reduction in the risk of any level of oral mucositis in favour of KGF: RR 0.71, 95% CI 0.60 to 0.85; 215 participants ([Analysis 1.1](#)).

Four studies, one at low ([Vadhan-Raj 2010](#)), and three at unclear risk of bias ([Bradstock 2014](#); [Meropol 2003](#); [Rosen 2006](#)), showed a reduction in the risk of moderate to severe oral mucositis in favour of KGF: RR 0.56, 95% CI 0.45 to 0.70; 344 participants ([Analysis 1.2](#)).

Three studies, one at low ([Vadhan-Raj 2010](#)), and two at unclear risk of bias ([Bradstock 2014](#); [Rosen 2006](#)), showed a reduction in the risk of severe oral mucositis in favour of KGF: RR 0.30, 95% CI 0.14 to 0.65; 263 participants ([Analysis 1.3](#)).

Interruptions to cancer treatment

Adults receiving radiotherapy to the head and neck with cisplatin/fluorouracil (5FU)

There was insufficient evidence from three studies, two at low ([Henke 2011](#); [Le 2011](#)), and one at unclear risk of bias ([Brizel 2008](#)), to determine whether or not KGF reduces the risk of having unscheduled radiotherapy breaks of five or more days: RR 1.01, 95% CI 0.65 to 1.59; 473 participants ([Analysis 1.4](#)).

There was insufficient evidence, from the same two studies at low risk of bias, to determine whether or not KGF reduces the risk of having chemotherapy delays/discontinuations: RR 0.96, 95% CI 0.62 to 1.47; 374 participants ([Analysis 1.5](#)).

Oral pain

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

There was insufficient evidence, from one study at low risk of bias ([Freytes 2004](#)), to determine whether or not KGF reduces the mean worst pain experienced on a 0 (no pain) to 10 (worst pain) scale: mean difference (MD) -0.85, 95% CI -3.00 to 1.30; 42 participants ([Analysis 1.6](#)).

Adults receiving radiotherapy to the head and neck with cisplatin

There was some evidence, from two studies at low risk of bias ([Henke 2011](#); [Le 2011](#)), that KGF might lead to a reduction in the mean pain score on a 0 (no pain) to 4 (worst pain) scale: MD -0.12, 95% CI -0.27 to 0.02; 374 participants ([Analysis 1.6](#)).

Normalcy of diet

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

There was insufficient evidence from four studies, one at low ([Blijlevens 2013](#)), two at unclear ([Jagasia 2012](#); [Spielberger 2004](#)), and one at high risk of bias ([Fink 2011](#)), to determine whether or not KGF reduces the risk of total parenteral nutrition: RR 0.89, 95% CI 0.58 to 1.34; 714 participants ([Analysis 1.7](#)).

There was further insufficient evidence, from one study at low risk of bias ([Freytes 2004](#)), to determine whether or not KGF reduces the mean worst ability to eat score on a 1 (normal) to 4 (no solids or liquids) scale: MD -0.50, 95% CI -1.21 to 0.21; 42 participants ([Analysis 1.8](#)).

Adults receiving radiotherapy to the head and neck with cisplatin/fluorouracil (5FU)

There was insufficient evidence from three studies, two at low ([Henke 2011](#); [Le 2011](#)), and one at unclear risk of bias ([Brizel 2008](#)), to determine whether or not KGF reduces the risk of receiving supplemental nutrition (total parenteral nutrition, percutaneous endoscopic gastrostomy, nasogastric tube or intravenous (IV) hydration): RR 1.03, 95% CI 0.77 to 1.37; 473 participants ([Analysis 1.7](#)).

Adverse events

This outcome was difficult to summarise due to poor and inconsistent reporting, and we did not meta-analyse any data. However, there do not appear to be any serious concerns regarding adverse effects of KGF. We have tabulated relevant information in Additional [Table 1](#).

Number of days in hospital

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

There was insufficient evidence, from one study at low risk of bias ([Blijlevens 2013](#)), to determine whether or not KGF reduces the mean number of days in hospital: MD 0.00, 95% CI -1.64 to 1.64; 281 participants ([Analysis 1.9](#)).

Number of days of treatment with opioid analgesics

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

There was some imprecise evidence, from two studies at low risk of bias ([Blijlevens 2013](#); [Freytes 2004](#)), that KGF might lead to a reduction in the mean number of days of treatment with opioid analgesics: MD -1.41, 95% CI -3.33 to 0.51; 323 participants ([Analysis 1.10](#)). The average effect is around 1.5 days reduction, but the confidence interval is compatible with both a reduction of almost 3.5 days and an increase of half a day.

No studies assessed the outcomes 'quality of life' and 'number of days unable to take medicine orally'.

Keratinocyte growth factor (KGF) dose comparisons

There was some inconsistent evidence from which no conclusions can be drawn regarding different dosages of KGF ([Analysis 2.1](#); [Analysis 2.2](#); [Analysis 2.3](#); [Analysis 2.4](#); [Analysis 2.5](#); [Analysis 2.6](#); [Analysis 2.7](#); [Analysis 2.8](#)).

Keratinocyte growth factor (KGF) versus chlorhexidine

One study, at high risk of bias and analysing 90 children receiving mixed chemotherapy alone for acute lymphoblastic leukaemia ([Gholizadeh 2016](#)), compared KGF by IV infusion with chlorhexidine mouthwash. There was weak evidence (due to risk of bias and low sample size) that KGF performs better than chlorhexidine in reducing the risk of any level of oral mucositis (RR 0.67, 95% CI 0.54 to 0.85; [Analysis 3.1](#)), moderate to severe oral mucositis (RR 0.12, 95% CI 0.05 to 0.28; [Analysis 3.2](#)), and severe oral mucositis (RR 0.01, 95% CI 0.00 to 0.19; [Analysis 3.3](#)).

Granulocyte-macrophage colony-stimulating factor (GM-CSF) versus placebo/no treatment

Oral mucositis

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for mixed cancers

There was some evidence, from one study at low risk of bias (Dazzi 2003), that GM-CSF might lead to a reduction in the risk of any level of oral mucositis: RR 0.91, 95% CI 0.80 to 1.04; 90 participants (Analysis 4.1).

There was insufficient evidence, from one study at unclear risk of bias (Nemunaitis 1995), to determine whether or not GM-CSF reduces the risk of moderate to severe oral mucositis: RR 0.94, 95% CI 0.79 to 1.13; 109 participants (Analysis 4.2).

There was insufficient evidence from three studies, one at low (Dazzi 2003), and two at unclear risk of bias (Nemunaitis 1995; van der Lelie 2001), to determine whether or not GM-CSF reduces the risk of severe oral mucositis: RR 0.74, 95% CI 0.33 to 1.67; 235 participants (Analysis 4.3).

Adults receiving radiotherapy to the head and neck

There was insufficient evidence, from one study at high risk of bias (McAleese 2006), to determine whether or not GM-CSF reduces the risk of any level of oral mucositis (RR 1.01, 95% CI 0.82 to 1.23; 29 participants; Analysis 4.1), moderate to severe oral mucositis (RR 0.72, 95% CI 0.49 to 1.06; 29 participants; Analysis 4.2), or severe oral mucositis (RR 0.31, 95% CI 0.01 to 7.09; 29 participants; Analysis 4.3).

Adults receiving chemotherapy alone for mixed cancers

There was insufficient evidence from two studies, one at unclear (Cartee 1995), and one at high risk of bias (Chi 1995), to determine whether or not GM-CSF reduces the risk of severe oral mucositis: RR 0.59, 95% CI 0.05 to 7.11; 65 participants (Analysis 4.3).

Oral pain

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for mixed cancers

There was insufficient evidence, from one study at low risk of bias (Dazzi 2003), to determine whether or not GM-CSF reduces the mean pain score on a 0 (no pain) to 10 (worst pain) scale: MD 0.60, 95% CI -0.85 to 2.05; 90 participants (Analysis 4.4).

Normalcy of diet

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

There was insufficient evidence, from one study at unclear risk of bias (van der Lelie 2001), to determine whether or not GM-CSF

reduces the risk of total parenteral nutrition: RR 1.10, 95% CI 0.63 to 1.91; 36 participants (Analysis 4.5).

Adults receiving radiotherapy to the head and neck

There was insufficient evidence, from one study at high risk of bias (McAleese 2006), to determine whether or not GM-CSF reduces the risk of tube feeding: RR 0.31, 95% CI 0.01 to 7.09; 29 participants (Analysis 4.5).

Adverse events

This outcome was difficult to summarise due to poor and inconsistent reporting, and we did not meta-analyse any data. However, there do not appear to be any serious concerns regarding adverse effects of GM-CSF. We have tabulated relevant information in Additional Table 2.

Number of days of treatment with opioid analgesics

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for mixed cancers

There was some evidence, from one study at low risk of bias (Dazzi 2003), that GM-CSF might lead to a reduction in the mean number of days of treatment with opioid analgesics: MD -1.10, 95% CI -1.91 to -0.29; 90 participants (Analysis 4.6).

No studies assessed the outcomes 'interruptions to cancer treatment', 'quality of life', 'number of days in hospital' and 'number of days unable to take medicine orally'.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) dose comparison

There is some very weak evidence, from one study at unclear risk of bias and analysing 36 adults receiving mixed chemotherapy alone for breast cancer (Cartee 1995), that a higher dose of GM-CSF (range 1260 µg to 12,600 µg) reduces the risk of severe oral mucositis when compared to a lower dose (range 12.6 µg to 126 µg): RR 2.75, 95% CI 1.07 to 7.04; 36 participants (Analysis 5.1).

Granulocyte-macrophage colony-stimulating factor (GM-CSF) versus sucralfate

One study, at low risk of bias and analysing 40 adults receiving radiotherapy to the head and neck (Saarilahti 2002), compared GM-CSF with sucralfate, both as a mouthwash. There was insufficient evidence to determine whether GM-CSF or sucralfate perform better in reducing the risk of moderate to severe oral mucositis (RR 0.96, 95% CI 0.80 to 1.14; Analysis 6.1), severe oral mucositis (RR 0.54, 95% CI 0.24 to 1.21; Analysis 6.2), interruptions to cancer treatment (RR 0.13, 95% CI 0.01 to 2.36; Analysis 6.3),

or percutaneous endoscopic gastrostomy (RR 0.18, 95% CI 0.01 to 3.56; [Analysis 6.4](#)).

Granulocyte-colony stimulating factor (G-CSF) versus placebo/no treatment

Oral mucositis

Adults receiving radiotherapy to the head and neck

There was insufficient evidence, from two studies at low risk of bias ([Schneider 1999](#); [Su 2006](#)), to determine whether or not G-CSF reduces the risk of any level of oral mucositis: RR 1.02, 95% CI 0.86 to 1.22; 54 participants ([Analysis 7.1](#)).

The same two studies showed weak evidence (due to a wide confidence interval and low sample size) of a reduction in the risk of severe oral mucositis in favour of G-CSF: RR 0.37, 95% CI 0.15 to 0.87; 54 participants ([Analysis 7.3](#)).

Adults receiving chemotherapy alone for mixed cancers

One study on lung cancer, at unclear risk of bias ([Crawford 1999](#)), showed a reduction in the risk of any level of oral mucositis in favour of G-CSF: RR 0.59, 95% CI 0.40 to 0.87; 195 participants ([Analysis 7.1](#)).

One study on breast cancer, at high risk of bias ([Katano 1995](#)), showed very weak evidence (due to risk of bias, very low sample size and a wide confidence interval) of a reduction in the risk of moderate to severe oral mucositis in favour of G-CSF: RR 0.33, 95% CI 0.12 to 0.95; 14 participants ([Analysis 7.2](#)).

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

One study, at high risk of bias and analysing 121 participants ([Linch 1993](#)), did not provide any details of how oral mucositis was measured, so it is not clear what severity the information refers to. There were no numerical results reported, only the statement: "There was no difference in the frequency of stomatitis (defined as a sore, infected or ulcerated mouth, lips or pharynx), the incidence being between 29 and 33% in all groups" (Additional [Table 3](#)).

Interruptions to cancer treatment

Adults receiving radiotherapy to the head and neck

There was insufficient evidence, from one study at low risk of bias ([Su 2006](#)), to determine whether or not G-CSF reduces the risk of radiotherapy interruptions: RR 0.22, 95% CI 0.01 to 4.31; 40 participants ([Analysis 7.4](#)).

Normalcy of diet

Adults receiving radiotherapy to the head and neck

There was insufficient evidence, from one study at low risk of bias ([Su 2006](#)), to determine whether or not G-CSF reduces the risk of percutaneous endoscopic gastrostomy: RR 0.16, 95% CI 0.01 to 2.86; 40 participants ([Analysis 7.5](#)).

Adverse events

This outcome was difficult to summarise due to poor and inconsistent reporting, and we did not meta-analyse any data. However, there do not appear to be any serious concerns regarding adverse effects of G-CSF. We have tabulated relevant information in Additional [Table 4](#).

No studies assessed the outcomes 'oral pain', 'quality of life', 'number of days in hospital', 'number of days of treatment with opioid analgesics' and 'number of days unable to take medicine orally'.

G-CSF (pegfilgrastim) versus G-CSF (filgrastim)

There was insufficient evidence, from one study at high risk of bias and analysing 61 children receiving bone marrow/stem cell transplantation after conditioning therapy for mixed cancers ([Cesaro 2013](#)), to determine whether pegfilgrastim or filgrastim perform better in reducing the risk of any level of oral mucositis (RR 1.02, 95% CI 0.82 to 1.27; [Analysis 8.1](#)), moderate to severe oral mucositis (RR 0.78, 95% CI 0.55 to 1.11; [Analysis 8.2](#)), or total parenteral nutrition (RR 1.00, 95% CI 0.94 to 1.06; [Analysis 8.3](#)).

Epidermal growth factor (EGF) versus placebo

Oral mucositis

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

There was insufficient evidence, from one study at low risk of bias and analysing 136 participants ([Kim 2017](#)), to determine whether or not EGF reduces the risk of moderate to severe oral mucositis (RR 1.06, 95% CI 0.78 to 1.43; [Analysis 9.1](#)), or severe oral mucositis (RR 1.03, 95% CI 0.59 to 1.80; [Analysis 9.2](#)).

Adults receiving radiotherapy to the head and neck with/without cisplatin

One study, at high risk of bias ([Wu 2009](#)), showed weak evidence (due to risk of bias and low sample size) of a reduction in the risk of moderate to severe oral mucositis in favour of EGF: RR 0.67, 95% CI 0.45 to 0.99; 103 participants ([Analysis 9.1](#)).

Interruptions to cancer treatment

Adults receiving radiotherapy to the head and neck with/without cisplatin

There was insufficient evidence, from one study at high risk of bias (Wu 2009), to determine whether or not EGF reduces the risk of having radiotherapy breaks longer than two days: RR 4.38, 95% CI 0.25 to 75.44; 113 participants (Analysis 9.3).

Normalcy of diet

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

There was insufficient evidence, from one study at low risk of bias (Kim 2017), to determine whether or not EGF reduces the risk of total parenteral nutrition: RR 1.03, 95% CI 0.55 to 1.94; 136 participants (Analysis 9.4).

Adverse events

There do not appear to be any serious concerns regarding adverse effects of EGF. We have tabulated relevant information in Additional Table 5.

No studies assessed the outcomes 'oral pain', 'quality of life', 'number of days in hospital', 'number of days of treatment with opioid analgesics' and 'number of days unable to take medicine orally'.

Intestinal trefoil factor (ITF) versus placebo

Oral mucositis

Adults receiving chemotherapy alone for colorectal cancer

One study, at unclear risk of bias and analysing 99 participants (Peterson 2009), showed weak evidence (due to low sample size) of a reduction in the risk of any level of oral mucositis (RR 0.52, 95% CI 0.35 to 0.79; Analysis 10.1), and moderate to severe oral mucositis (RR 0.22, 95% CI 0.10 to 0.48; Analysis 10.2), both in favour of ITF.

There was insufficient evidence, from the same study, to determine whether or not EGF reduces the risk of severe oral mucositis: RR 1.52, 95% CI 0.06 to 36.39 (Analysis 10.3).

Adverse events

There do not appear to be any serious concerns regarding adverse effects of ITF. We have tabulated relevant information in Additional Table 6.

No studies assessed the outcomes 'interruptions to cancer treatment', 'oral pain', 'quality of life', 'normalcy of diet', 'number of days in hospital', 'number of days of treatment with opioid analgesics' and 'number of days unable to take medicine orally'.

Intestinal trefoil factor (ITF) dose comparison

There was insufficient evidence, from one study at unclear risk of bias and analysing 66 adults receiving chemotherapy alone for colorectal cancer (Peterson 2009), to determine whether a lower dose (336 mg) or a higher dose (2688 mg) perform better in reducing the risk of oral mucositis of any severity (Analysis 11.1; Analysis 11.2; Analysis 11.3).

Erythropoietin versus placebo

Oral mucositis

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

One study, at low risk of bias and analysing 80 participants (Hosseinjani 2017), showed weak evidence (due to low sample size) of a reduction in the risk of any level of oral mucositis (RR 0.35, 95% CI 0.21 to 0.60; Analysis 12.1), and moderate to severe oral mucositis (RR 0.43, 95% CI 0.24 to 0.79; Analysis 12.2), both in favour of erythropoietin.

The same study showed weak evidence (due to low sample size and a wide confidence interval) that erythropoietin might reduce the risk of severe oral mucositis, but there is also some possibility of an increase in risk: RR 0.40, 95% CI 0.14 to 1.17 (Analysis 12.3).

Number of days in hospital

Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers

There was insufficient evidence, from one study at low risk of bias (Hosseinjani 2017), to determine whether or not erythropoietin reduces the mean number of days in hospital: MD -2.95, 95% CI -7.73 to 1.83; 80 participants (Analysis 12.4).

No studies assessed the outcomes 'interruptions to cancer treatment', 'oral pain', 'quality of life', 'normalcy of diet', 'adverse events', 'number of days of treatment with opioid analgesics' and 'number of days unable to take medicine orally'.

Transforming growth factor (TGF) versus placebo

Oral mucositis

Adults receiving chemotherapy alone for colorectal cancer

There was insufficient evidence, from one study at high risk of bias and analysing 13 participants ([Antoun 2009](#)), to determine

whether or not TGF reduces the risk of any level of oral mucositis: RR 0.10, 95% CI 0.01 to 1.71 (Additional [Table 7](#)).

No studies assessed the outcomes 'interruptions to cancer treatment', 'oral pain', 'quality of life', 'normalcy of diet', 'adverse events', 'number of days in hospital', 'number of days of treatment with opioid analgesics' and 'number of days unable to take medicine orally'.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

GM-CSF compared to placebo/no treatment for preventing oral mucositis in adults with cancer receiving treatment						
Patient or population: adults** receiving treatment for cancer (see subgroup for treatment type) Setting: hospital Intervention: GM-CSF Comparison: placebo/no treatment						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with GM-CSF treatment				
Oral mucositis (moderate + severe)	BMT/SCT after conditioning for haematological cancers		RR 0.94 (0.79 to 1.13)	109 (1 study)	⊕○○○ VERY LOW ¹	There is insufficient evidence to determine a benefit for GM-CSF in this population NNTB = 20 (95% CI 6 NNTB to 10 NNTH)
	839 per 1000	789 per 1000 (663 to 948)				
	RT to head and neck		RR 0.72 (0.49 to 1.06)	29 (1 study)	⊕○○○ VERY LOW ²	There is insufficient evidence to determine a benefit for GM-CSF in this population NNTB = 4 (95% CI 3 NNTB to 14 NNTH)
	929 per 1000	669 per 1000 (455 to 984)				
Oral mucositis (severe)	BMT/SCT after conditioning for mixed cancers		RR 0.74 (0.33 to 1.67)	235 (3 studies)	⊕⊕○○ LOW ³	There is insufficient evidence to determine a benefit for GM-CSF in this population NNTB = 12 (95% CI 5 NNTB to 5 NNTH)
	347 per 1000	257 per 1000 (115 to 580)				

	RT to head and neck	RR 0.31 (0.01 to 7.09)	29 (1 study)	⊕○○○ VERY LOW ⁴	There is insufficient evidence to determine a benefit for GM-CSF in
	71 per 1000 22 per 1000 (1 to 506)				
	CT alone for mixed cancers	RR 0.59 (0.05 to 7.11)	65 (2 studies)	⊕○○○ VERY LOW ⁵	There is insufficient evidence to determine a benefit for GM-CSF in
	500 per 1000 295 per 1000 (25 to 1000)				
Adverse events	Adverse events that were attributed to the study drugs rather than the cancer therapy were typically bone pain, nausea, fever and headache. Events were not reported as being serious. Some studies did not report adverse events and 1 even reported that there were none. However, reporting was poor and inconsistent, meaning that it was not appropriate to meta-analyse data				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**There were no studies conducted on children.

***The number of people that would need to receive GM-CSF in order to prevent 1 additional person from developing the outcome. Calculated as 1 divided by the absolute risk reduction (which is the control arm event rate minus the experimental arm event rate). NNTH means the number of people that would need to receive GM-CSF to cause 1 additional person to develop the outcome. All decimal places have been rounded up to the nearest whole number (i.e. 6.1 = 7).

BMT: bone marrow transplantation; **CI:** confidence interval; **CT:** chemotherapy; **GM-CSF:** granulocyte-macrophage colony-stimulating factor; **NNTB:** number needed to treat to benefit***; **NNTH:** number needed to treat to harm; **RR:** risk ratio; **RT:** radiotherapy; **SCT:** stem cell transplantation.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Downgraded by 2 levels for imprecision (single study with a small sample size and the confidence interval includes a possible increase in risk that is of a similar magnitude to the possible reduction in risk); downgraded 1 further level for indirectness (single study so not widely generalisable).

²Downgraded by 2 levels for imprecision (wide confidence interval and very small sample size); downgraded by 1 further level for high risk of performance bias; downgraded by 1 further level for indirectness (single study so not widely generalisable); downgraded by 1 further level for publication bias as there are 2 references in [Studies awaiting classification](#) that would be included in the RT to head and neck subgroup, but the data are not currently available ([Antonadou 1998](#); [NCT00293462](#)).

³Downgraded by 2 levels for imprecision (small sample size and the confidence interval includes a possible increase in risk that is of a similar magnitude to the possible reduction in risk); downgraded by 1 further level for inconsistency (substantial heterogeneity: $I^2 = 50\%$ to 90% , $P < 0.1$).

⁴Downgraded by 2 levels for imprecision (extremely wide confidence interval incorporating both very large increase and reduction in risk, very small sample size and very low event rate); downgraded by 1 further level for high risk of performance bias; downgraded by 1 further level for indirectness (single study so not widely generalisable); downgraded by 1 further level for publication bias as there are 2 references in [Studies awaiting classification](#) that would be included in the RT to head and neck subgroup, but the data are not currently available ([Antonadou 1998](#); [NCT00293462](#)).

⁵Downgraded by 2 levels for imprecision (extremely wide confidence interval incorporating both very large increase and reduction in risk and very small sample size); downgraded by 1 further level for high risk of performance bias; downgraded by 1 further level for inconsistency (substantial heterogeneity: $I^2 = 50\%$ to 90% , $P < 0.1$).

G-CSF compared to placebo/no treatment for preventing oral mucositis in patients with cancer receiving treatment						
Patient or population: adults** receiving treatment for cancer (see subgroup for treatment type) Setting: hospital Intervention: G-CSF Comparison: placebo/no treatment						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo/no treatment	Risk with G-CSF				
Oral mucositis (moderate + severe)	CT alone for breast cancer		RR 0.33 (0.12 to 0.95)	14 (1 study)	⊕○○○ VERY LOW ¹	There is very weak evidence that there might be a benefit for G-CSF in this population NNTB = 2 (95% CI 2 to 20)
	1000 per 1000	330 per 1000 (120 to 950)				
Oral mucositis (severe)	RT to head and neck		RR 0.37 (0.15 to 0.87)	54 (2 studies)	⊕⊕○○ LOW ²	There is weak evidence that there might be a benefit for G-CSF in this population NNTB = 3 (95% CI 3 to 15)
	519 per 1000	192 per 1000 (78 to 451)				
Adverse events	There was limited evidence of adverse events for G-CSF. 2 of the 6 studies did not report adverse events. There were low rates of mild to moderate events, the most common of which appeared to be bone pain. However, reporting was poor and inconsistent, meaning that it was not appropriate to meta-analyse data					

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**There were no studies conducted on children.

***The number of people that would need to receive G-CSF in order to prevent 1 additional person from developing the outcome. Calculated as 1 divided by the absolute risk reduction (which is the control arm event rate minus the experimental arm event rate). NNTH means the number of people that would need to receive G-CSF to cause 1 additional person to develop the outcome. All decimal places have been rounded up to the nearest whole number (i.e. 6.1 = 7).

CI: confidence interval; CT: chemotherapy; G-CSF: granulocyte-colony stimulating factor; NNTB: number needed to treat to benefit***; NNTH: number needed to treat to harm; RR: risk ratio; RT: radiotherapy.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

¹Downgraded by 2 levels for imprecision (wide confidence interval and very small sample size); downgraded by 1 further level for high risk of performance bias; downgraded by 1 further level for indirectness (single study so not widely generalisable).

²Downgraded by 2 levels for imprecision (wide confidence interval and very small sample size).

DISCUSSION

Summary of main results

Thirty-five studies met our eligibility criteria and were included in this review. We used GRADE methodology to assess the quality of the body of evidence for each of the main comparisons and for the primary outcome of incidence and severity of oral mucositis (GRADE 2004). Most of the evidence we found was for keratinocyte growth factor (KGF: [Summary of findings for the main comparison](#)), granulocyte-macrophage colony-stimulating factor (GM-CSF: [Summary of findings 2](#)), and granulocyte-colony stimulating factor (G-CSF: [Summary of findings 3](#)).

Our main findings were as follows.

Keratinocyte growth factor (KGF)

Moderate to severe oral mucositis

- Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancer: might be a reduction in risk (11% and ranging from 20% to 1%).
- Adults receiving radiotherapy to the head and neck with cisplatin/fluorouracil (5FU): probably a reduction in risk (9% and ranging from 17% to no reduction).
- Adults receiving chemotherapy alone for mixed cancers: likely to be a reduction in risk (44% and ranging from 55% to 30%).

Severe oral mucositis

- Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancer: might be a reduction in risk, but some possibility of an increase in risk (15% reduction and ranging from 35% reduction to 11% increase).
- Adults receiving radiotherapy to the head and neck with cisplatin/fluorouracil (5FU): very likely a reduction in risk (21% and ranging from 31% to 10%).
- Adults receiving chemotherapy alone for mixed cancers: might be a reduction in risk (60% and ranging from 86% to 35%).

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

Moderate to severe oral mucositis

- Adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancer: insufficient evidence of a benefit.
- Adults receiving radiotherapy to the head and neck: insufficient evidence of a benefit.

Severe oral mucositis

- Adults receiving bone marrow/stem cell transplantation after conditioning therapy for mixed cancers: insufficient evidence of a benefit.
- Adults receiving radiotherapy to the head and neck: insufficient evidence of a benefit.
- Adults receiving chemotherapy alone for mixed cancers: insufficient evidence of a benefit.

Granulocyte-colony stimulating factor (G-CSF)

Moderate to severe oral mucositis

- Adults receiving chemotherapy alone for breast cancer: very weak evidence of a possible reduction in risk (67% and ranging from 88% to 5%).

Severe oral mucositis

- Adults receiving radiotherapy to the head and neck: weak evidence of a possible reduction in risk (63% and ranging from 85% to 13%).

The remaining evidence for the primary outcome was from single-study comparisons.

- Epidermal growth factor might reduce the risk of moderate to severe oral mucositis in adults receiving radiotherapy to the head and neck with or without cisplatin, but there was insufficient evidence of a reduction in the risk of either moderate to severe, or severe oral mucositis in adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancer.
- Intestinal trefoil factor might reduce the risk of moderate to severe oral mucositis in adults receiving chemotherapy alone for colorectal cancer.
- Erythropoietin might reduce the risk of moderate to severe oral mucositis in adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancer.

There was mostly insufficient evidence of a benefit regarding the secondary outcomes of this review. The interventions investigated all appear to be relatively safe, with only mild to moderate adverse effects reported.

Overall completeness and applicability of evidence

The evidence we have presented in this review allows for some conclusions to be made regarding the effects of KGF for preventing oral mucositis in adults receiving certain types of cancer treatment. However, the evidence is lacking for other cytokines and

growth factors, and for children. It is unfortunate that the two studies we found on KGF versus placebo in children were unclear in their reporting and we were unable to present any data. All studies reported on our primary outcome, but the evidence for the secondary outcomes of this review is lacking.

The evidence for KGF should have reasonable external validity as most of the adult population were covered in terms of the types of treatment people have for different types of cancer. The studies were also carried out all over the world and often involved multiple sites. One limitation, however, may be the fact that most studies were done in middle-income and high-income countries, so may be less generalisable to people in low-income countries.

Numerous studies reported on some of our secondary outcomes but did not report the data in a suitable format for inclusion in our meta-analyses e.g. as median with or without range, area under the curve, or as mean (or a graph) but with no standard deviation/standard error/P value. In such cases, the meta-analysis is biased by missing information. However, the Cochrane risk of bias tool and meta-analyses do not currently address this issue adequately. The study may be assessed at high risk of selective outcome reporting, but if the study is not included in the meta-analysis due to having no data, then this is not reflected or accounted for. This highlights the need for standardisation in both 'what to measure' and 'how to measure it' in clinical trials in this area of research. Otherwise there will continue to be research waste, with data that are not able to be pooled in data syntheses. There are initiatives such as COMET (Core Outcome Measures in Effectiveness Trials) and COSMIN (CONsensus-based Standards for the selection of health Measurement INSTRuments) that can help with these issues, and future research in these areas would be beneficial.

During the systematic review process, we developed further concerns regarding the usefulness of the secondary outcomes because it was not clear whether or not they were due to oral mucositis. Hospitalisation, the use of supplemental nutrition or opioid analgesics, and interruptions to cancer treatment could all occur due to reasons other than oral mucositis. Furthermore, it was not always clear if adverse effects were due to the interventions given to prevent oral mucositis. These issues could be improved by clearer and more explicit reporting.

Cost is an issue that we did not consider in this review, but it is one that may affect whether or not the evidence can be applied in some settings. Taking KGF as an example, cost per dose is high but there is currently an absence of high quality health economic evaluations, rendering decision making difficult.

Quality of the evidence

We included 35 randomised controlled trials (RCTs) analysing 3102 participants. Despite this large volume of research, we were not able to make robust conclusions about the effects of most cytokines and growth factors. The strongest body of evidence, both in terms of volume and quality, was for the different populations

receiving KGF. We assessed the evidence for KGF in preventing severe oral mucositis in adults receiving radiotherapy to the head and neck with or without cisplatin or fluorouracil as high quality. In the same population, we downgraded the evidence for prevention of moderate to severe oral mucositis by one level due to inconsistency in the individual study results (heterogeneity), resulting in moderate-quality evidence. In adults receiving chemotherapy alone for mixed cancers, we downgraded the evidence for KGF in preventing moderate to severe oral mucositis once due to publication bias, as we found an unpublished study that would be included in the meta-analysis, resulting in moderate-quality evidence ([NCT00393822](#)). In the same population, we downgraded the evidence for prevention of severe oral mucositis by two levels: one for publication bias and one for imprecision due to a small sample size, low event rates and a wide confidence interval. This resulted in low-quality evidence. In adults receiving bone marrow/stem cell transplantation after conditioning therapy for haematological cancers, the evidence for KGF in preventing both moderate to severe and severe oral mucositis was assessed as low quality. We downgraded the evidence by two levels: one for heterogeneity and one for publication bias, as there were two studies for which we could not find published full reports ([NCT02313792](#); [Spielberger 2001](#)). There were no concerns over risk of bias in the KGF studies as they are often large multicentre trials which are carried out well, mostly using placebos for blinding purposes, and with very low attrition.

The evidence for GM-CSF and G-CSF was weaker, and consequently was rated as being low or very low quality. The reasons for downgrading were mostly due to imprecision because the volume of evidence was much lower and the studies often recruited very few participants, leading to very wide confidence intervals that frequently included both the possibility of a decrease in risk and an increase. Further reasons were risk of performance bias due to lack of blinding in some of these studies, inconsistency, and also because some of the evidence was from single studies. When a body of evidence was from a single study, we automatically downgraded a level. The reasoning behind this was because often, when using GRADE methodology, bodies of evidence are downgraded for inconsistency due to different effect estimates in the individual studies. This inconsistency is not possible for a single-study body of evidence and therefore not downgrading would falsely inflate the rating of quality, whilst at the same time the larger body of evidence is unfairly penalised, in comparison, due to having more studies. In such cases, we downgraded the single-study evidence due to indirectness as it may only be generalisable to the particular population who took part in the study.

The remaining evidence for other interventions was from single-study comparisons and therefore was all considered to be of low to very low quality, mainly for indirectness (as described above) and imprecision.

Potential biases in the review process

Although systematic review methodology is designed to minimise biases in the process, decisions are often made out of necessity or for practical reasons, and this can introduce some potential bias. Once we began to assess the literature identified by the searches, we became concerned that we may have missed some relevant studies because we had not included search terms for other conditions for which cytokines and growth factors have been used to manage (e.g. diarrhoea, graft-versus-host disease, and neutropenia). In order to assess the extent of this potential problem, a rough scoping search was run including the search terms. The yield was very high and a single review author assessed a sample of 500 records, but no further studies were identified. Therefore, we decided not to amend the search by adding the new search terms. We acknowledge the possibility that we have missed some studies that have measured and reported on oral mucositis but not mentioned it in the abstract. This could introduce bias if there are relevant data missing from the review.

There were some studies that had multiple treatment arms with different doses of the cytokine or growth factor. In all instances, we combined the arms to make a pairwise comparison against the control arm thus losing some possible subtleties of the data and potentially biasing the results.

Agreements and disagreements with other studies or reviews

The Mucositis Study Group (MSG) of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) is the leading international group in this area of research. In 2013, they published a series of systematic reviews on the different interventions for managing oral mucositis, including one on cytokines and growth factors (Raber-Durlacher 2013). These reviews feed into the MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy (Lalla 2014). The MASCC/ISOO systematic review is not limited to RCTs. The current guidance from this group is as follows.

- Recommendations in favour of an intervention (i.e. strong evidence supporting effectiveness): the panel *recommends* that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to *prevent* oral mucositis (at a dose of 60 µg/kg per day for three days prior to conditioning treatment and for three days after transplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a haematological malignancy (level II evidence).
- Suggestions against an intervention (i.e. weaker evidence indicating lack of effectiveness): the panel *suggests* that granulocyte-macrophage colony-stimulating factor mouthwash *not* be used to *prevent* oral mucositis in patients receiving high-

dose chemotherapy, for autologous or allogeneic stem cell transplantation (level II evidence).

For our meta-analyses for KGF in the above mentioned population, we combined studies of all types of KGF, both with autologous and allogeneic transplants, and with total body irradiation (TBI), without TBI or a mixture of TBI/no TBI. The MASCC/ISOO systematic review separated all of these factors. However, looking at the individual studies in our meta-analyses, the first recommendation appears to be a valid one. Furthermore, the MASCC/ISOO systematic review states “Evidence on the efficacy of palifermin in autologous HSCT without TBI conditioning is conflicting...and these rather small studies did not allow a guideline. In addition, no guideline could be provided for the use of palifermin in the setting of allogeneic HSCT with or without TBI.” Despite our meta-analyses including some further RCTs not included in the other review, these statements also appear to be valid.

The suggestion against GM-CSF mouthwash is also a valid one as, although we did not separate studies by mode of administration, it is clear that the two mouthwash studies in our analysis (Analysis 4.3) have conflicting results. However, based on one study on GM-CSF given intravenously in this population (Nemunaitis 1995), there is promising evidence of a benefit, but the MASCC/ISOO systematic review considered this evidence alongside other studies that we did not include, and concluded that there was no guideline possible.

Our results are not in agreement with the following statements from the MASCC/ISOO systematic review regarding other populations receiving KGF.

- “No guideline could be provided for the use of palifermin in the setting of CT for solid and hematological tumors...due to insufficient evidence.”
- “In addition, no guideline could be provided for the use of palifermin in H&N RT due to insufficient evidence.”

We present some moderate- to high-quality evidence of a benefit for KGF in these populations, possibly warranting new guideline statements in their next update. This evidence would equate to level I evidence in the grading system used in the guidelines (“evidence obtained from meta-analysis of multiple, well-designed, controlled studies”). In another Cochrane Review on preventing salivary gland dysfunction in patients receiving radiotherapy to the head and neck, with or without chemotherapy, KGF did not appear to have any detrimental effect on overall survival or progression-free survival (Riley 2017).

AUTHORS' CONCLUSIONS

Implications for practice

We are confident that keratinocyte growth factor (KGF) is bene-

ficial in the prevention of oral mucositis in adults who are receiving: a) radiotherapy to the head and neck with cisplatin or fluorouracil; or b) chemotherapy alone for mixed solid and haematological cancers. We are less confident about a benefit for KGF in adults receiving bone marrow/stem cell transplant after conditioning therapy for haematological cancers because of multiple factors involved in that population, such as whether or not they received total body irradiation (TBI) and whether the transplant was autologous (the patients' own cells) or allogeneic (cells from a donor). KGF appears to be a relatively safe intervention.

Due to limited research, we are not confident that there are any beneficial effects of other cytokines and growth factors. There is currently insufficient evidence to draw any conclusions about the use of cytokines and growth factors in children.

Implications for research

Despite a large volume of research, once studies are categorised by cancer treatment type/population, there is very little we can conclude regarding the effects of most cytokines and growth factors. It is clear that much more research is needed in this area, especially as many of the interventions have shown promise in some populations, yet we have not been able to make robust conclusions due to the limited volume/low sample sizes. Strong evidence from randomised controlled trials (RCTs) using placebos should be generated before head-to-head comparisons of different interventions are undertaken. More RCTs of KGF are needed in the population receiving bone marrow/stem cell transplant after conditioning therapy so that in future updates we may be able to include separate subgroups to account for differing factors such as TBI/no TBI and autologous/allogeneic transplant. Further large confirmatory RCTs of KGF would be beneficial in the other two populations: a) radiotherapy to the head and neck with chemotherapy (and possibly without chemotherapy); and b) chemotherapy alone for mixed cancers.

More research is needed on all other cytokines and growth factors in the various populations, including in children. Placebo controls

should be used in the first instance to establish whether or not they are effective, and only then should head-to-head comparisons of active interventions be made.

Future RCTs should be adequately powered to detect a difference if one actually exists and they should be reported according to the CONSORT Statement (Consolidated Standards of Reporting Trials). They should measure and report in full all the outcomes listed in this review, most of which are recommended in the core outcome set produced by Bellm et al (Bellm 2002). For our primary outcome of oral mucositis incidence, we urge trialists to use a measurement tool such as the WHO (World Health Organization) or NCI-NCT (National Cancer Institute common toxicity criteria) scale (Appendix 9), to allow us to combine the data with those already included in this review. Reporting the maximum grade of oral mucositis experienced per participant would allow us to assess the incidence of different severities, thus maximising the usefulness of the data. It would also be useful if oral pain was measured on a 0 to 10 scale and reported as an overall mean and mean maximum score experienced per participant. Numbers included in any analysis should always be reported and any continuous data should be reported as means and standard deviations. Furthermore, measurement of outcomes should be taken with appropriate frequency so as to avoid any problems with ascertainment bias.

ACKNOWLEDGEMENTS

We would like to thank the Cochrane Oral Health editorial team (in particular, Tanya Walsh, Laura MacDonald and Janet Lear) for their help in preparing this Cochrane Review. We also thank Joanne Elliott for her comments on our search strategy. We thank external referees Andrei Barasch and Douglas E Peterson (Please note that referees provided comments on a personal basis and not as representatives of any organisation with which they are connected.)

REFERENCES

References to studies included in this review

Antoun 2009 {published data only}

Antoun S, Boige V, Ducreux M, Paintain M, van't Hof M, Enslen M, et al. Protective effect of an enteral formula containing TGF-beta(2) in the prevention of chemotherapy-induced diarrhoea: a pilot study. *e-SPEN, European e-Journal of Clinical Nutrition and Metabolism* 2009;4(6): e348–50.

Blazar 2006 {published data only}

Blazar BR, Weisdorf DJ, Defor T, Goldman A, Braun T, Silver S, et al. Phase 1/2 randomized, placebo-control trial

of palifermin to prevent graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). *Blood* 2006;108(9):3216–22.

Blijlevens 2013 {published data only}

Blijlevens N, de Chateau M, Krivan G, Rabitsch W, Szomor A, Pytik R, et al. In a high-dose melphalan setting, palifermin compared to placebo had no effect on oral mucositis or related patient's burden. *Supportive Care in Cancer* 2011;19(Suppl 2):S227–8.

Blijlevens N, de Chateau M, Krivan G, Rabitsch W, Szomor A, Pytik R, et al. Medical resource use of two different dosing regimens of palifermin to prevent mucositis in

- multiple myeloma patients receiving one-day administration of high-dose melphalan. *Bone Marrow Transplantation* 2011;**46**(Suppl 1s):S163–4.
- Blijlevens N, de Chateau M, Krivan G, Rabitsch W, Szomor A, Pytik R, et al. Randomized controlled trial of two different dosing regimens of palifermin to prevent mucositis in multiple myeloma patients receiving one-day administration of high-dose melphalan. *Blood* 2010;**116**(21):904.
- * Blijlevens N, de Chateau M, Krivan G, Rabitsch W, Szomor A, Pytik R, et al. In a high-dose melphalan setting, palifermin compared with placebo had no effect on oral mucositis or related patient's burden. *Bone Marrow Transplantation* 2013;**48**(7):966–71.
- Bradstock 2014** {published data only}
- Bradstock KF, Link E, Collins M, Di Iulio J, Lewis ID, Schwarer A, et al. A randomized trial of prophylactic palifermin on gastrointestinal toxicity after intensive induction therapy for acute myeloid leukaemia. *British Journal of Haematology* 2014;**167**(5):618–25.
- Brizel 2008** {published data only}
- Brizel DM, Murphy BA, Rosenthal DI, Pandya KJ, Glück S, Brizel HE, et al. Phase II study of palifermin and concurrent chemoradiation in head and neck squamous cell carcinoma. *Journal of Clinical Oncology* 2008;**26**(15):2489–96.
- Cartee 1995** {published data only}
- Cartee L, Petros WP, Rosner G, Gilbert C, Moore S, Affronti M, et al. Evaluation of GM-CSF mouthwash for prevention of chemotherapy-induced mucositis: a randomized double-blind dose escalating study. *Blood* 1993;**82**(10 Suppl 1):496a. Abs No 1968]
- * Cartee L, Petros WP, Rosner GL, Gilbert C, Moore S, Affronti ML, et al. Evaluation of GM-CSF mouthwash for prevention of chemotherapy-induced mucositis: a randomized, double-blind, dose-ranging study. *Cytokine* 1995;**7**(5):471–7.
- Cesaro 2013** {published data only}
- * Cesaro S, Nesi F, Tridello G, Abate M, Panizzolo IS, Balter R, et al. A randomized, non-inferiority study comparing efficacy and safety of a single dose of pegfilgrastim versus daily filgrastim in pediatric patients after autologous peripheral blood stem cell transplant. *PLOS One* 2013;**8**(1):e53252.
- Cesaro S, Nesi F, Tridello G, Fagioli F, Abate M, Panizzolo I, et al. A non-inferiority study comparing efficacy and safety of a single dose of pegfilgrastim versus daily filgrastim in paediatric patients after autologous peripheral blood stem cell transplant. *Bone Marrow Transplantation* 2012;**47**(Suppl 1s):S372.
- Chi 1995** {published data only}
- * Chi KH, Chen CH, Chan WK, Chow KC, Chen SY, Yen SH, et al. Effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients after cisplatin, fluorouracil and leucovorin chemotherapy. *Journal of Clinical Oncology* 1995;**13**(10):2620–8.
- Chi KH, Chen CH, Chan WK, Yen SH, Liang MJ, Chou KC, et al. Effect of granulocyte-macrophage colony-stimulating factor (GH-CFS) on oral mucositis in head and neck cancer patients after cisplatin, 5-FU and leucovorin chemotherapy. *Proceedings of the American Society of Clinical Oncology* 1994;**13**:428. Abs No 1469]
- Crawford 1999** {published data only}
- Crawford J, Glaspy J, Vincent M, Tomita D, Mazanet R. Effect of filgrastim (r-metHuG-CSF) on oral mucositis in patients with small cell lung cancer (SCLC) receiving chemotherapy (cyclophosphamide, doxorubicin and etoposide, CAE). *Proceedings of the American Society of Clinical Oncology* 1994;**13**:442. Abs No A1523]
- Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *New England Journal of Medicine* 1991;**325**(3):164–70.
- * Crawford J, Tomita DK, Mazanet R, Glaspy J, Ozer H. Reduction of oral mucositis by filgrastim (r-metHuG-CSF) in patients receiving chemotherapy. *Cytokines, Cellular and Molecular Therapy* 1999;**5**(4):187–93.
- Dazzi 2003** {published data only}
- * Dazzi C, Cariello A, Giovanis P, Monti M, Vertogen B, Leoni M, et al. Prophylaxis with GM-CSF mouthwashes does not reduce frequency and duration of severe oral mucositis in patients with solid tumors undergoing high-dose chemotherapy with autologous peripheral blood stem cell transplantation rescue: a double-blind, randomized, placebo-controlled study. *Annals of Oncology* 2003;**14**(4):559–63.
- Dazzi C, Cariello A, Monti M, Giovanis P, Vertogen B, Nanni O, et al. Prophylaxis with GM-CSF mouthwash does not reduce frequency and duration of severe oral mucositis in patients with solid tumors undergoing high dose chemotherapy with autologous PBPC rescue: a double-blind randomized placebo-controlled study. *Annals of Oncology* 2002;**13** Suppl 5:167. Abs No 617O]
- Fink 2011** {published and unpublished data}
- Fink G, Ihorst G, Burbeck M, Kleber M, Kohlweyer U, Engelhardt M. Prospective randomized trial of palifermin (keratinocyte growth factor) versus best supportive care measures (BSC) for the decrease of oral mucositis (OM) in lymphoma patients receiving high-dose BEAM-(BCNU, Etoposide, Ara-C, Melphalan) conditioning and autologous stem-cell transplantation (ASCT). *Onkologie. Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Onkologie*; 2011 Sept-Oct 30-04; Basel (Switzerland). Basel (Switzerland): S Karger AG, 2011:302.
- Freytes 2004** {published data only}
- Freytes CO, Ratanatharathorn V, Taylor C, Abboud C, Chesser N, Restrepo A, et al. Phase I/II randomized trial evaluating the safety and clinical effects of repifermin administered to reduce mucositis in patients undergoing

- autologous hematopoietic stem cell transplantation. *Clinical Cancer Research* 2004;**10**(24):8318–24.
- Gholizadeh 2016** *{published data only}*
Gholizadeh N, Mehdipoor M, Sajadi H, Moosavi MS. Palifermin and chlorhexidine mouthwashes in prevention of chemotherapy-induced mucositis in children with acute lymphocytic leukemia: a randomized controlled trial. *Journal of Dentistry (Shiraz, Iran)* 2016;**17**(4):343–7.
- Henke 2011** *{published data only}*
* Henke M, Alfonsi M, Foa P, Giralt J, Bardet E, Cerezo L, et al. Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: a randomized, placebo-controlled trial. *Journal of Clinical Oncology* 2011;**29**(20):2815–20.
Henke M, Alfonsi M, Foa P, Giralt J, Bardet E, Cerezo L, et al. Palifermin significantly reduces severe oral mucositis in subjects with resected locally advanced head and neck cancer undergoing post-operative concurrent radio-chemotherapy. *Radiotherapy and Oncology* 2008;**88** Suppl 2:S152.
- Hosseiniyani 2017** *{published data only}*
Hosseiniyani H, Hadjibabae M, Gholami K, Javadi M, Radfar M, Jahangard-Rafsanjani Z, et al. The efficacy of erythropoietin mouthwash in prevention of oral mucositis in patients undergoing autologous hematopoietic SCT: a double-blind, randomized, placebo-controlled trial. *Hematological Oncology* 2017;**35**(1):106–12.
- Jagasia 2012** *{published data only}*
Jagasia MH, Abonour R, Long GD, Bolwell BJ, Laport GG, Shore TB, et al. Palifermin for the reduction of acute GVHD: a randomized, double-blind, placebo-controlled trial. *Bone Marrow Transplantation* 2012;**47**(10):1350–5.
- Katano 1995** *{published data only}*
Katano M, Nakamura M, Matsuo T, Iyama A, Hisatsugu T. Effect of granulocyte colony-stimulating factor (G-CSF) on chemotherapy-induced oral mucositis. *Surgery Today* 1995; **25**(3):202–6.
- Kim 2017** *{published data only}*
Kim J-W, Kim KI, Lee HJ, Kim B-S, Bang S-M, Kim I, et al. Interim analysis of randomized phase II study of recombinant human epidermal growth factor on oral mucositis induced by intensive chemotherapy with stem cell transplantation for hematologic malignancies. *Blood* 2010; **116**(21):905.
* Kim JW, Kim MG, Lee HJ, Koh Y, Kwon JH, Kim I, et al. Topical recombinant human epidermal growth factor for oral mucositis induced by intensive chemotherapy with hematopoietic stem cell transplantation: final analysis of a randomized, double-blind, placebo-controlled, phase 2 trial. *PLOS One* 2017;**12**(1):e0168854.
Kim KI, Kim JW, Lee HJ, Kim BS, Bang SM, Kim I, et al. Recombinant human epidermal growth factor on oral mucositis induced by intensive chemotherapy with stem cell transplantation. *American Journal of Hematology* 2013;**88** (2):107–12.
- Le 2011** *{published data only}*
Le Q, Kim H, Schneider C, Muraközy G, Skladowski K, Reinisch S, et al. Palifermin reduces severe oral mucositis in subjects with locally advanced head and neck cancer undergoing chemoradiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 2008;**72** Suppl 1:S32.
* Le QT, Kim HE, Schneider CJ, Muraközy G, Skladowski K, Reinisch S, et al. Palifermin reduces severe mucositis in definitive chemoradiotherapy of locally advanced head and neck cancer: a randomized, placebo-controlled study. *Journal of Clinical Oncology* 2011;**29**(20):2808–14.
- Linch 1993** *{published data only}*
Linch DC, Scarffe H, Proctor S, Chopra R, Taylor PR, Morgenstern G, et al. Randomised vehicle-controlled dose-finding study of glycosylated recombinant human granulocyte colony-stimulating factor after bone marrow transplantation. *Bone Marrow Transplantation* 1993;**11**(4): 307–11.
- Lucchese 2016a** *{published data only}*
Lucchese A, Matarese G, Ghislanzoni LH, Gastaldi G, Manuelli M, Gherlone E. Efficacy and effects of palifermin for the treatment of oral mucositis in patients affected by acute lymphoblastic leukemia. *Leukemia and Lymphoma* 2016;**57**(4):820–7.
- Lucchese 2016b** *{published data only}*
Lucchese A, Matarese G, Manuelli M, Ciuffreda C, Bassani L, Isola G, et al. Reliability and efficacy of palifermin in prevention and management of oral mucositis in patients with acute lymphoblastic leukemia: a randomized, double-blind controlled clinical trial. *Minerva Stomatologica* 2016; **65**(1):43–53.
- Makkonen 2000** *{published data only}*
* Makkonen TA, Minn H, Jekunen A, Vilja P, Tuominen J, Joensuu H. Granulocyte macrophage-colony stimulating factor (GM-CSF) and sucalfate in prevention of radiation-induced mucositis: a prospective randomized study. *International Journal of Radiation Oncology, Biology, Physics* 2000;**46**(3):525–34.
Minn HR, Makkonen TA, Jekunen A, Vilja P, Tuominen J, Joensuu H. Granulocyte macrophage-colony stimulating factor (GM-CSF) and sucalfate in prevention of radiation-induced mucositis: a prospective randomized study. *International Journal of Radiation Oncology, Biology, Physics* 1999;**45** Suppl 3:239.
- McAleese 2006** *{published data only}*
McAleese JJ, Bishop KM, A'Hern R, Henk JM. Randomized phase II study of GM-CSF to reduce mucositis caused by accelerated radiotherapy of laryngeal cancer. *British Journal of Radiology* 2006;**79**(943):608–13.
- Meropol 2003** *{published data only}*
Meropol NJ, Somer RA, Gutheil J, Pelley RJ, Modiano MR, Rowinsky EK, et al. Randomized phase I trial of recombinant human keratinocyte growth factor plus chemotherapy: potential role as mucosal protectant. *Journal of Clinical Oncology* 2003;**21**(8):1452–8.

Nemunaitis 1995 {published data only}

Nemunaitis J, Rosenfeld CS, Ash R, Freedman MH, Deeg HJ, Appelbaum F, et al. Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. *Bone Marrow Transplantation* 1995;**15**(6):949–54.

Peterson 2009 {published data only}

Barker NP, Peterson DE, Akhmadullina LI, Rodionova I, Sherman NZ, Gertner JM, et al. Prophylaxis of recurrent chemotherapy-induced oral mucositis: a phase II multicenter, randomized, placebo-controlled trial of recombinant human intestinal trefoil factor (rhITF). *Journal of Clinical Oncology* 2008;**26**:505. Abs No 9514]

* Peterson DE, Barker NP, Akhmadullina LI, Rodionova I, Sherman NZ, Davidenko IS, et al. Phase II, randomized, double-blind, placebo-controlled study of recombinant human intestinal trefoil factor oral spray for prevention of oral mucositis in patients with colorectal cancer who are receiving fluorouracil-based chemotherapy. *Journal of Clinical Oncology* 2009;**27**(26):4333–8.

Rosen 2006 {published data only}

Clarke SJ, Abdi E, Davis ID, Schnell FM, Zalcberg JR, Gutheil J, et al. Recombinant human keratinocyte growth factor (rHuKGF) prevents chemotherapy-induced mucositis in patients with advanced colorectal cancer: a randomized phase II trial. *Proceedings of the American Society of Clinical Oncology* 2001;**20** (Pt 1):383a. Abs No 1529]

* Rosen LS, Abdi E, Davis ID, Gutheil J, Schnell FM, Zalcberg J, et al. Palifermin reduces the incidence of oral mucositis in patients with metastatic colorectal cancer treated with fluorouracil-based chemotherapy. *Journal of Clinical Oncology* 2006;**24**(33):5194–200.

Saarilahti 2002 {published data only}

Saarilahti K, Kajanti M, Joensuu T, Kouri M, Joensuu H. Comparison of granulocyte-macrophage colony-stimulating factor and sucalfate mouthwashes in the prevention of radiation-induced mucositis: a double-blind prospective randomized phase III study. *International Journal of Radiation Oncology, Biology, Physics* 2002;**54**(2):479–85.

Schneider 1999 {published data only}

Schneider SB, Nishimura RD, Zimmerman RP, Tran L, Shiplacoff J, Tormey M, et al. Filgrastim (r-metHuG-CSF) and its potential use in the reduction of radiation-induced oropharyngeal mucositis: an interim look at a randomized, double-blind, placebo-controlled trial. *Cytokines, Cellular and Molecular Therapy* 1999;**5**(3):175–80.

Spielberger 2004 {published data only}

Emmanouilides C, Spielberger R, Stiff P, Rong A, Isitt J, Bensinger W, et al. Palifermin treatment of mucositis in transplant patients reduces health resource use: phase III results. *Journal of Supportive Oncology* 2004;**2**(2):77–8. Spielberger R, Emmanouilides C, Stiff P, Bensinger W, Gentile T, Weisdorf D, et al. Use of recombinant human keratinocyte growth factor (palifermin) can reduce severe oral mucositis in patients with hematologic malignancies undergoing autologous peripheral blood progenitor cell

transplantation after radiation-based conditioning. *Journal of Supportive Oncology* 2004;**2**(2):73–4.

* Spielberger R, Stiff P, Bensinger W, Gentile T, Weisdorf D, Kewalramani T, et al. Palifermin for oral mucositis after intensive therapy for hematologic cancers. *New England Journal of Medicine* 2004;**351**(25):2590–8.

Stiff P, Bensinger W, Emmanouilides C, Gentile T, Weisdorf D, Shea T, et al. Treatment of mucositis with palifermin improves patient function and results in a clinically meaningful reduction in mouth and throat soreness: phase III results. *Journal of Supportive Oncology* 2004;**2**(2):75–6.

Stiff PJ, Emmanouilides C, Bensinger WI, Gentile T, Blazar B, Shea TC, et al. Palifermin reduces patient-reported mouth and throat soreness and improves patient functioning in the hematopoietic stem-cell transplantation setting. *Journal of Clinical Oncology* 2006;**24**(33):5186–93.

Su 2006 {published data only}

Su YB. Double-blind, randomized trial of granulocyte-colony stimulating factor (G-CSF) versus (v) placebo during postoperative radiation (RT) for advanced resectable squamous cell head and neck cancer (SCCHN): impact on mucositis. *Journal of Clinical Oncology* 2004;**22** Suppl:14S.

* Su YB, Vickers AJ, Zelefsky MJ, Kraus DH, Shaha AR, Shah JP, et al. Double-blind, placebo-controlled, randomized trial of granulocyte-colony stimulating factor during postoperative radiotherapy for squamous head and neck cancer. *Cancer Journal* 2006;**12**(3):182–8.

Vadhan-Raj 2010 {published data only}

* Vadhan-Raj S, Trent J, Patel S, Zhou X, Johnson MM, Araujo D, et al. Single-dose palifermin prevents severe oral mucositis during multicycle chemotherapy in patients with cancer: a randomised trial. *Annals of Internal Medicine* 2010;**153**(6):358–67.

Vadhan-Raj S, Trent JC, Patel SR, Araujo DM, Ludwig LA, Bailey D, et al. Randomized, double-blind, placebo-controlled study of palifermin for the prevention of mucositis in patients receiving doxorubicin-based chemotherapy. *Journal of Clinical Oncology* 2008;**26**(15 Suppl):9547.

van der Lelie 2001 {published data only}

van der Lelie H, Thomas BL, van Oers RH, Ek-Post M, Sjamsoedin SA, van Dijk-Overtom ML, et al. Effect of locally applied GM-CSF on oral mucositis after stem cell transplantation: a prospective placebo-controlled double-blind study. *Annals of Hematology* 2001;**80**(3):150–4.

Wu 2009 {published data only}

Ahn Y, Wu H, Song S, Kim Y, Oh Y, Lee C, et al. The therapeutic effect of recombinant human epidermal growth factor (rhEGF) on mucositis in patients with head and neck cancer undergoing radiotherapy with or without chemotherapy: a double-blind placebo-controlled prospective phase II multi-institutional study. *Journal of Clinical Oncology* 2008;**26**(15 Suppl):6021.

Lee S, Song S, Kim Y, Oh Y, Lee C, Keum K, et al. The therapeutic effect of recombinant human epidermal growth factor (rhEGF) on mucositis in patients with head and neck cancer undergoing radiotherapy with or

without chemotherapy: a double-blind placebo-controlled prospective phase II multi-institutional clinical trial. *International Journal of Radiation Oncology, Biology, Physics* 2008;**72**(1):S32.

* Wu HG, Song SY, Kim YS, Oh YT, Lee CG, Keum KC, et al. Therapeutic effect of recombinant human epidermal growth factor (RhEGF) on mucositis in patients undergoing radiotherapy, with or without chemotherapy, for head and neck cancer: a double-blind placebo-controlled prospective phase 2 multi-institutional clinical trial. *Cancer* 2009;**115** (16):3699–708.

References to studies excluded from this review

Antin 2002 {published data only}

Antin JH, Lee SJ, Neuberg D, Alyea E, Soiffer RJ, Sonis S, et al. A phase I/II double-blind, placebo-controlled study of recombinant human interleukin-11 for mucositis and acute GVHD prevention in allogeneic stem cell transplantation. *Bone Marrow Transplantation* 2002;**29**(5):373–7.

de Koning 2007 {published data only}

de Koning BA, Philipsen-Geerling B, Hoijs M, Hahlen K, Buller HA, Pieters R. Protection against chemotherapy induced mucositis by TGF-beta(2) in childhood cancer patients: results from a randomized cross-over study. *Pediatric Blood & Cancer* 2007;**48**(5):532–9.

Foncuberta 2001 {published data only}

Foncuberta MC, Cagnoni PJ, Brandts CH, Mandanas R, Fields K, Derigs HG, et al. Topical transforming growth factor-beta3 in the prevention or alleviation of chemotherapy-induced oral mucositis in patients with lymphomas or solid tumors. *Journal of Immunotherapy* 2001;**24**(4):384–8.

Gebbia 1994 {published data only}

Gebbia V, Valenza R, Testa A, Cannata G, Borsellino N, Gebbia N. A prospective randomized trial of thymopentin versus granulocyte-colony stimulating factor with or without thymopentin in the prevention of febrile episodes in cancer patients undergoing highly cytotoxic chemotherapy. *Anticancer Research* 1994;**14**(2B):731–4.

Gladkov 2013 {published data only}

Gladkov O, Buchner A, Bias P, Mueller U, Elsaesser R. Chemotherapy-associated treatment burden in breast cancer patients receiving lipegfilgrastim or pegfilgrastim: secondary efficacy data from a phase III study. *Haematologica* 2013;**98** (Suppl 1):426.

Gordon 1993 {published data only}

Gordon B, Spadinger A, Hodges E, Coccia P. Effect of granulocyte macrophage colony stimulating factor (GM-CSF) on oral mucositis after autologous bone marrow transplantation. *Proceedings of the American Society of Clinical Oncology* 1993;**12**:432. Abs No 1489]

Horsley 2007 {published data only}

Horsley P, Bauer JD, Mazkowiack R, Gardner R, Bashford J. Palifermin improves severe mucositis, swallowing problems, nutrition impact symptoms, and length of stay in patients

undergoing hematopoietic stem cell transplantation. *Supportive Care in Cancer* 2007;**15**(1):105–9.

Hunter 2009 {published data only}

Hunter A, Mahendra P, Wilson K, Fields P, Cook G, Peniker A, et al. A randomized, double-blind, placebo-controlled, multicenter trial of ATL-104, a swallowable mouthwash, in patients with oral mucositis following peripheral blood stem cell transplantation. *Journal of Supportive Oncology* 2007;**5** (4 Suppl 2):52–3.

* Hunter A, Mahendra P, Wilson K, Fields P, Cook G, Peniker A, et al. Treatment of oral mucositis after peripheral blood SCT with ATL-104 mouthwash: results from a randomized, double-blind, placebo-controlled trial. *Bone Marrow Transplantation* 2009;**43**(7):563–9.

Ifrah 1999 {published data only}

Ifrah N, Witz F, Jouet JP, Francois S, Lamy T, Linassier C, et al. Intensive short term therapy with granulocyte-macrophage-colony stimulating factor support, similar to therapy for acute myeloblastic leukemia, does not improve overall results for adults with acute lymphoblastic leukemia. *American Cancer Society* 1999;**86**(8):1496–505.

Iwase 1997 {published data only}

Iwase M, Yoshiya M, Kakuta S, Nagumo M. Clinical trial of recombinant granulocyte colony-stimulating factor for chemotherapy-induced neutropenia patients with oral cancer. *Journal of Oral and Maxillofacial Surgery* 1997;**55** (8):836–40.

Jones 1996 {published data only}

Jones SE, Schottstaedt MW, Duncan LA, Kirby RL, Good RH, Mennel RG, et al. Randomized double-blind prospective trial to evaluate the effects of sargramostim versus placebo in a moderate-dose fluorouracil, doxorubicin, and cyclophosphamide adjuvant chemotherapy program for stage II and III breast cancer. *Journal of Clinical Oncology* 1996;**14**(11):2976–83.

Karthus 1998 {published data only}

* Karthus M, Rosenthal C, Huebner G, Paul H, Elser C, Hertenstein B, et al. Effect of topical oral G-CSF on oral mucositis: a randomised placebo-controlled trial. *Bone Marrow Transplantation* 1998;**22**(8):781–5.
Karthus M, Rosenthal C, Paul H, Novotny J, Hóbnér G, Fenchel K, et al. Effect of topical oral G-CSF application on oral mucositis in high-grade lymphoma patients treated with hd-methotrexate (hd-mtx) - results of a randomized placebo-controlled trial. *Proceedings of the American Society of Clinical Oncology* 1998;**17**:235.

Kubo 2016 {published data only}

Kubo K, Miyazaki Y, Murayama T, Shimazaki R, Usui N, Urabe A, et al. A randomized, double-blind trial of pegfilgrastim versus filgrastim for the management of neutropenia during CHASE(R) chemotherapy for malignant lymphoma. *British Journal of Haematology* 2016; **174**(4):563–70.

Lee 2016 {published data only}

Lee KH, Kim JY, Lee MH, Han HS, Lim JH, Park KU, et al. A randomized, multicenter, phase II/III study to

determine the optimal dose and to evaluate the efficacy and safety of pegteogragstim (GCPGC) on chemotherapy-induced neutropenia compared to pegfilgrastim in breast cancer patients: KCSG PC10-09. *Supportive Care in Cancer* 2016;**24**(4):1709–17.

Legros 1997 {published data only}

Legros M, Fleury J, Bay JO, Choufi B, Basile M, Condat P, et al. rhGM-CSF vs placebo following rhGM-CSF-mobilized PBPC transplantation: a phase III double-blind randomized trial. *Bone Marrow Transplantation* 1997;**19**(3): 209–13.

Limaye 2013 {published data only}

* Limaye SA, Haddad RI, Cilli F, Sonis ST, Colevas AD, Brennan MT, et al. Phase 1b, multicenter, single blinded, placebo-controlled, sequential dose escalation study to assess the safety and tolerability of topically applied AG013 in subjects with locally advanced head and neck cancer receiving induction chemotherapy. *Cancer* 2013;**119**(24): 4268–76.

Murphy B, Limaye SA, Sonis ST, Cilli F, Brennan MT, Hu KS, et al. Phase 1B study assessing safety, tolerability and efficacy of AG013 in subjects with head and neck cancer receiving induction chemotherapy. *Supportive Care in Cancer* 2012;**20**(1 Suppl):S259. Abs No 1078]

Nabholtz 2002 {published data only}

Nabholtz JM, Cantin J, Chang J, Guevin R, Patel R, Tkaczuk K, et al. Phase III trial comparing granulocyte colony-stimulating factor to leridistim in the prevention of neutropenic complications in breast cancer patients treated with docetaxel/doxorubicin/cyclophosphamide: results of the BCIRG 004 trial. *Clinical Breast Cancer* 2002;**3**(4): 268–75.

NCT00360971 {published data only}

NCT00360971. Palifermin in lessening oral mucositis in patients undergoing radiation therapy and chemotherapy for locally advanced head and neck cancer [A randomized, phase III, double-blind, placebo-controlled study to evaluate the efficacy and safety of palifermin (NSC# 740548; IND # 6370) for the reduction of oral mucositis in patients with locally advanced head and neck cancer receiving radiation therapy with concurrent chemotherapy (followed by surgery for selected patients)]. clinicaltrials.gov/show/NCT00360971 (first received 3 August 2006).

NCT00626639 {published data only}

NCT00626639. A study of palifermin for the reduction of oral mucositis in patients with locally advanced head and neck cancer receiving postoperative radiotherapy and concurrent chemotherapy [A phase 1/2 study to evaluate safety, pharmacokinetics, pharmacodynamics and preliminary efficacy of weekly doses of palifermin (rHuKGF) for the reduction of oral mucositis in subjects with locally advanced head and neck cancer (HNC) receiving postoperative radiotherapy with concurrent chemotherapy]. clinicaltrials.gov/show/NCT00626639 (first received 21 February 2008).

Pettengell 1992 {published data only}

Pettengell R, Gurney H, Radford JA, Deakin DP, James R, Wilkinson PM, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood* 1992;**80**(6):1430–6.

Ryu 2007 {published data only}

Hoffman KE, Pugh SL, James JL, Scarantino C, Movsas B, Valicenti RK, et al. The impact of concurrent granulocyte-macrophage colony-stimulating factor on quality of life in head and neck cancer patients: results of the randomized, placebo-controlled Radiation Therapy Oncology Group 9901 trial. *Quality of Life Research* 2014;**23**(6):1841–58.
* Ryu JK, Swann S, LeVeque F, Scarantino CW, Johnson D, Chen A, et al. The impact of concurrent granulocyte macrophage-colony stimulating factor on radiation-induced mucositis in head and neck cancer patients: a double-blind placebo-controlled prospective phase III study by Radiation Therapy Oncology Group 9901. *International Journal of Radiation Oncology, Biology, Physics* 2007;**67**(3):643–50.

Throuvalas 1995 {published data only}

Throuvalas N, Antonadou D, Pulizzi M, Sarris G. Evaluation of the efficacy and safety of GM-CSF in the prophylaxis of mucositis in patients with head and neck cancer treated with RT. *European Journal of Cancer* 1995;**31** Suppl 5:S93. Abs No 431]

Tsurusawa 2016 {published data only}

Tsurusawa M, Watanabe T, Goshio M, Mori T, Mitsui T, Sunami S, et al. Randomized study of granulocyte colony stimulating factor for childhood B-cell non-Hodgkin lymphoma: a report from the Japanese pediatric leukemia/lymphoma study group B-NHL03 study. *Leukemia & Lymphoma* 2016;**57**(7):1657–64.

Vitale 2014 {published data only}

Vitale KM, Violago L, Cofnas P, Bishop J, Jin Z, Bhatia M, et al. Impact of palifermin on incidence of oral mucositis and healthcare utilization in children undergoing autologous hematopoietic stem cell transplantation for malignant diseases. *Pediatric Transplantation* 2014;**18**(2):211–6.

References to studies awaiting assessment

ACTRN12606000083594 {published data only}

ACTRN12606000083594. Safety and efficacy trial of whey growth factor extract for oral mucositis [A multicentre, double-blind, placebo-controlled, safety and efficacy trial of whey growth factor extract (WGFEA) for oral mucositis in lymphoma patients undergoing carmustine, etoposide, cytosine arabinoside and melphalan (BEAM) chemotherapy and autologous stem cell transplantation]. www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=1142 (first received 27 February 2006).

Antonadou 1998 {published data only}

Antonadou D, Athanassiou E, Synodinou M, Koliarakis N, Panoussaki K, Karageorgis P, et al. Evaluation of the efficacy of granulocyte macrophage colony stimulating factor (GM-

- CSF) in the prevention of radiation induced mucositis. *Radiotherapy and Oncology* 1998;**48** Suppl 1:S39.
- Elsaid 2001** *{published data only}*
Elsaid A, Farouk M. Significance of anemia and role of erythropoietin in radiation induced mucositis in head and neck cancer patients. *International Journal of Radiation Oncology, Biology, Physics* 2001;**51**(3 Suppl 1):368.
- Grzegorzczak 2006** *{published data only}*
* Grzegorzczak-Jazwinska A, Dwilewicz-Trojaczek J, Kozak I, Karakulska-Prystupiak E, Gorska R. Effect of locally applied G-CSF on oral mucositis after autogeneic and allogeneic stem cell transplantation. *Acta Haematologica Polonica* 2006;**37**(2):225–40.
Grzegorzczak-Jazwinska A, Dwilewicz-Trojaczek J, Kozak I, Karakulska-Prystupiak E, Gorska R. Effect of locally applied G-CSF on oral mucositis after autologous stem cell transplantation. *Dental and Medical Problems* 2004;**41**(4): 695–701.
- Koga 2015** *{published data only}*
Koga Y, Tsurusawa M, Watanabe T, Goshio M, Mori T, Mitsui T, et al. Randomized study of granulocyte colony stimulating factor for childhood B-cell non-Hodgkin lymphoma: a report from the Japanese pediatric leukemia/lymphoma study Group B-NHL03 study. *British Journal of Haematology* 2015;**171**(Suppl S1):63–4.
- NCT00293462** *{published data only}*
NCT00293462. GM-CSF mouthwash for preventing and treating mucositis in patients who are undergoing radiation therapy for head and neck cancer [Management of mucositis with GM-CSF (sargramostim) mouthwash study protocol]. clinicaltrials.gov/show/NCT00293462 (first received 16 February 2006).
- NCT00393822** *{published data only}*
NCT00393822. A study of palifermin for the reduction of oral mucositis in subjects with stage 2B or 3 locally advanced, colon cancer [A randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of palifermin (recombinant human keratinocyte growth factor) for reduction of oral mucositis in subjects with stage 2B or 3 locally advanced, colon cancer receiving 5-FU and leucovorin as adjuvant therapy]. clinicaltrials.gov/show/NCT00393822 (first received 26 October 2006).
- NCT02303197** *{published data only}*
NCT02303197. Clinical trial on the efficacy and safety of Chining decoction in the treatment of radiation stomatitis [A randomized, controlled clinical trial on the efficacy and safety of Chining decoction in the treatment of radiation stomatitis]. clinicaltrials.gov/show/NCT02303197 (first received 25 November 2014).
- NCT02313792** *{published data only}*
NCT02313792. Palifermin for patients receiving hematopoietic stem cell transplantation [Efficacy, safety and quality of life of palifermin on reducing oral mucositis in patients with hematopoietic stem cell transplantation, prospective double-blind randomized phase III trial]. clinicaltrials.gov/show/NCT02313792 (first received 5 December 2014).
- Patte 2002** *{published data only}*
Patte C, Laplanche A, Bertozzi AI, Baruchel A, Frappaz D, Schmitt C, et al. Granulocyte colony-stimulating factor in induction treatment of children with non-Hodgkin's lymphoma: a randomized study of the French Society of Pediatric Oncology. *Journal of Clinical Oncology* 2002;**20**(2):441–8.
- Schuster 2007a** *{published data only}*
Schuster MW, Anaissie E, Hurd D, Bensinger W, Mason J, McCarty J, et al. Final analysis of the phase II, randomized, double-blind, placebo-controlled trial of single-dose velfermin (CG53135-05) for the prevention of oral mucositis. *Journal of Supportive Oncology* 2007;**5**(4 Suppl 2):58–9.
- Schuster 2007b** *{published data only}*
Schuster MW, Mehta J, Waller EK, Rifkin RM, Micallef I, Hurd D, et al. A randomized placebo controlled phase II trial of prevention of severe oral mucositis using single dose velfermin in patients receiving myeloablative therapy and autologous hematopoietic stem cell transplant (AHSCT). *Blood* 2007;**110**(11):615.
- Shea 2007** *{published data only}*
Shea TC, Kewalramani T, Mun Y, Jayne G, Dreiling LK. Evaluation of single-dose palifermin to reduce oral mucositis (OM) in fractionated total body irradiation (FTBI) and high dose (HD) chemotherapy with autologous peripheral blood progenitor cell (PBPC) transplantation. *Blood* 2006;**108**(11 Part 1):875–6.
* Shea TC, Kewalramani T, Mun Y, Jayne G, Dreiling LK. Evaluation of single-dose palifermin to reduce oral mucositis in fractionated total-body irradiation and high-dose chemotherapy with autologous peripheral blood progenitor cell transplantation. *Journal of Supportive Oncology* 2007;**5**(4 Suppl 2):60–2.
- Spielberger 2001** *{published data only}*
Spielberger RT, Stiff P, Emmanouilides C, Yanovich S, Bensinger W, Hedrick E, et al. Efficacy of recombinant human keratinocyte growth factor (rHuKGF) in reducing mucositis in patients with hematologic malignancies undergoing autologous peripheral blood progenitor cell transplantation (auto-PBPCT) after radiation-based conditioning - results of a phase 2 trial. *Proceedings of the American Society of Clinical Oncology* 2001;**20**(Pt 1):7a. Abs No 25]

Additional references

- Al-Dasooqi 2013**
Al-Dasooqi N, Sonis ST, Bowen JM, Bateman E, Blijlevens N, Gibson RJ, et al. Emerging evidence on the pathobiology of mucositis. *Supportive Care in Cancer* 2013;**21**(11): 3233–41.
- Bellm 2002**
Bellm LA, Cunningham G, Durnell L, Eilers J, Epstein JB, Fleming T, et al. Defining clinically meaningful outcomes

- in the evaluation of new treatments for oral mucositis: oral mucositis patient provider advisory board. *Cancer Investigation* 2002;**20**(5-6):793–800.
- Boers-Doets 2013**
Boers-Doets CB, Raber-Durlacher JE, Treister NS, Epstein JB, Arends AB, Wiersma DR, et al. Mammalian target of rapamycin inhibitor-associated stomatitis. *Future Oncology* 2013;**9**(12):1883–92.
- Clarke 2007**
Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials* 2007;**8**:39.
- Dwan 2008**
Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. *PLOS One* 2008;**3**(8):e3081.
- Egger 1997**
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.
- Elting 2008**
Elting LS, Keefe DM, Sonis ST, Garden AS, Spijkervet FK, Barasch A, et al. Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. *Cancer* 2008;**113**(10):2704–13.
- Epstein 1999**
Epstein JB, Emerton S, Kolbinson DA, Le ND, Phillips N, Stevenson-Moore P, et al. Quality of life and oral function following radiotherapy for head and neck cancer. *Head & Neck* 1999;**21**(1):1–11.
- GRADE 2004**
Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.
- Higgins 2011**
Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.
- Jensen 2014**
Jensen SB, Peterson DE. Oral mucosal injury caused by cancer therapies: current management and new frontiers in research. *Journal of Oral Pathology and Medicine* 2014;**43**(2):81–90.
- Lalla 2008**
Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dental Clinics of North America* 2008;**52**(1):61–77.
- Lalla 2014**
Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer* 2014;**120**(10):1453–61.
- Lefebvre 2011**
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.
- Lyman 2010**
Lyman GH, Dale DC, Wolff DA, Culakova E, Poniewierski MS, Kuderer NM, et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. *Journal of Clinical Oncology* 2010;**28**(17):2914–24.
- Miller 2001**
Miller M, Kearney N. Oral care for patients with cancer: a review of the literature. *Cancer Nursing* 2001;**24**(4):241–54.
- Nonzee 2008**
Nonzee NJ, Dandade NA, Patel U, Markossian T, Agulnik M, Argiris A, et al. Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis. *Cancer* 2008;**113**(6):1446–52.
- Peterson 2015**
Peterson DE, Srivastava R, Lalla RV. Oral mucosal injury in oncology patients: perspectives on maturation of a field. *Oral Diseases* 2015; Vol. 21, issue 2:133–41.
- Raber-Durlacher 2013**
Raber-Durlacher JE, von Bültzingslöwen I, Logan RM, Bowen J, Al-Azri AR, Everaus H, et al. Systematic review of cytokines and growth factors for the management of oral mucositis in cancer patients. *Supportive Care in Cancer* 2013;**21**(1):343–55.
- Riley 2017**
Riley P, Glenny AM, Hua F, Worthington HV. Pharmacological interventions for preventing dry mouth and salivary gland dysfunction following radiotherapy. *Cochrane Database of Systematic Reviews* 2017, Issue 7. [DOI: 10.1002/14651858.CD012744]
- Scully 2006**
Scully C, Sonis S, Diz PD. Oral mucositis. *Oral Diseases* 2006;**12**(3):229–41.
- Sonis 2001**
Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *Journal of Clinical Oncology* 2001;**19**(8):2201–5.
- Sonis 2004**
Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 2004;**100**(9 Suppl):1995–2025.

Sonis 2009

Sonis ST. Mucositis: the impact, biology and therapeutic opportunities of oral mucositis. *Oral Oncology* 2009;**45**(12):1015–20.

Trotti 2003

Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiotherapy and Oncology* 2003;**66**(3): 253–62.

Turhal 2000

Turhal NS, Erdal S, Karacay S. Efficacy of treatment to relieve mucositis-induced discomfort. *Supportive Care in Cancer* 2000;**8**(1):55–8.

von Bültzingslöwen 2006

von Bültzingslöwen I, Brennan MT, Spijkervet FK, Logan R, Stringer A, Raber-Durlacher JE, et al. Growth factors and cytokines in the prevention and treatment of oral and gastrointestinal mucositis. *Supportive Care in Cancer* 2006; **14**(6):519–27.

Williamson 2005

Williamson PR, Gamble C, Altman DG, Hutton JL. Outcome selection bias in meta-analysis. *Statistical Methods in Medical Research* 2005;**14**(5):515–24.

Williamson 2012

Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, et al. Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;**13**:132.

Worthington 2015

Worthington H, Clarkson J, Weldon J. Priority oral health research identification for clinical decision-making. *Evidence-based Dentistry* 2015;**16**(3):69–71.

References to other published versions of this review**Riley 2015**

Riley P, Glenny AM, Worthington HV, Littlewood A, Clarkson JE, McCabe MG. Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors. *Cochrane Database of Systematic Reviews* 2015, Issue 12. [DOI: 10.1002/14651858.CD011990]

Worthington 2011

Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, et al. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: 10.1002/14651858.CD000978.pub5]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Antoun 2009

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Institut Gustave Roussy, Villejuif, France</p> <p>Number of centres: 1</p> <p>Study duration: February 2005 to September 2006</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: adults with metastatic colorectal adenocarcinoma (grade 3 to 4); life expectancy greater than 3 months; receiving 5FU-based chemotherapy</p> <p>Exclusion criteria: HIV; pregnant or lactating; unlikely to comply with interventions; participation in another trial in the previous 12 months (unless regarding chemotherapeutic protocols); undergone a total colectomy; state of subocclusion; chronic inflammatory diseases of the digestive tract; radiation enteropathy</p> <p>Cancer type: metastatic colorectal adenocarcinoma (grade 3 to 4)</p> <p>Cancer treatment: 5FU-based chemotherapy</p> <p>Age at baseline (years): median 60 (not reported by group)</p> <p>Gender: not reported</p> <p>Number randomised: 22 (not reported by group)</p> <p>Number evaluated: 13 (Group A: 9; Group B: 4)</p>
Interventions	<p>Comparison: TGF-beta(2) versus placebo</p> <p>Group A: nutritional supplement of proteins, carbohydrates, fats, vitamins and minerals, with TGF-beta(2) (2 ng/mg protein); formulas were in powder form, mixed with cool previously boiled water at 0.23 g/mL (100 kcal/100 mL); during each cycle participants received 750 mL to 1000 mL per day plus any other food desired; formula administered for 2 days before, 2 days during, and 3 days after chemotherapy (7 days/cycle)</p> <p>Group B: same as above without the TGF-beta(2)</p> <p>Compliance: "Nine randomised patients who never ate the formula were excluded from the study" (not reported by group)</p> <p>Duration of treatment: "3 months (test or control formula), for a minimum of one and a maximum of eight cycles of treatment"</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale (no details reported on who assessed this, or when it was assessed; only reports incidence of any mucositis) • Chemotherapy-induced diarrhoea (not an outcome of this review)
Notes	<p>Sample size calculation: not reported</p> <p>Funding: "This study was funded by Nestec Ltd" - Nestlé (manufacturer of the intervention)</p> <p>Declarations/conflicts of interest: 6 of the 9 authors were either consultants (1) or employees (5) of Nestlé</p> <p>Data handling by review authors: reported in additional table</p> <p>Other information of note: "Due to low accrual of patients (22 patients were enrolled and randomised in 18 months), the study was prematurely stopped"</p>

Antoun 2009 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned" Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly assigned" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" and "The test formula differed only by containing an additional..." Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind" Comment: it is not clear who was blinded. There are subjective elements to the assessment of oral mucositis using this scale, requiring the patient's assessment of pain/soreness and their ability to swallow but, as the participants were unaware of their group allocation, the assessment of oral mucositis can be considered to be blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall attrition was 41% although it was not reported by group
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Blazar 2006

Methods	Trial design: parallel (7 arms) dose-ranging study Location: Universities of Minnesota and Michigan, USA Number of centres: 2 Study duration: not reported Trials registry number: none/unknown
---------	--

Participants	<p>Inclusion criteria: aged 3 to 65 years; diagnosed with haematological malignancy (including myelodysplastic syndromes); ECOG score of 0 to 2; eligible for allogeneic HSCT after conditioning treatment with chemotherapy with or without TBI</p> <p>Exclusion criteria: received previous allogeneic HSCT; due to receive a T-cell-depleted donor graft; active chronic skin disease; pre-existent inflammatory bowel disease; uncontrolled (antibiotic-resistant) bacterial infection; hepatitis; HIV</p> <p>Cancer type: haematologic: ALL (Group A: 12%; Group B: 3%); AML (Group A: 35%; Group B: 39%); CML (Group A: 10%; Group B: 26%); MDS (Group A: 9%; Group B: 19%); NHL (Group A: 19%; Group B: 3%); Hodgkin's (Group A: 1%; Group B: 0%); Other (Group A: 14%; Group B: 10%)</p> <p>Cancer treatment: both centres had allogeneic HSCT on day 0 but differed in conditioning regimen and GVHD prophylaxis as follows:</p> <ul style="list-style-type: none"> • Minnesota centre (n = 54): conditioning with cyclophosphamide (60 mg/kg per day for 2 days) on days -7 and -6 and TBI (total dose 13.2 Gy, fractionated as 165 cGy twice daily for 4 days) on days -4 to -1; GVHD prophylaxis with methotrexate (15 mg/m², IV bolus on day +1, and 10 mg/m², IV bolus on days 3, 6, and 11) and cyclosporine A (starting from day -3); Group A: 69%; Group B: 31% • Michigan centre (n = 46): conditioning with busulfan (1 mg/kg per dose given 4 times daily for 4 days) on days -8 to -5 and cyclophosphamide (60 mg/kg per day for 2 days) on days -3 and -2; GVHD prophylaxis with methotrexate (15 mg/m², IV bolus on day +1, and 10 mg/m², IV bolus on days 3, 6, and 11) and tacrolimus or cyclosporine A (starting from day -3); Group A: 70%; Group B: 30% <p>Both centres received G-CSF (filgrastim) 5 µg/kg per day from 24 hours after HSCT until neutrophil recovery</p> <p>Age at baseline (years): Group A: median 46 (range 7 to 65); Group B: median 46 (range 7 to 63)</p> <p>Gender: both groups 58% male</p> <p>Number randomised: 100 (Group A: 69; Group B: 31)</p> <p>Number evaluated: 96 (Group A: 65; Group B: 31)</p>
Interventions	<p>Comparison: KGF (palifermin) versus placebo (4 KGF arms and 3 placebo arms were each combined into a single arm)</p> <p>Group A: KGF</p> <ul style="list-style-type: none"> • (n = 8): 40 µg/kg per day in 6 doses on days -11, -10, -9 and 0, 1, 2 (total dose = 240 µg/kg) • (n = 10): 60 µg/kg per day in 6 doses on days -11, -10, -9 and 0, 1, 2 (total dose = 360 µg/kg) • (n = 14): 60 µg/kg per day in 9 doses on days -11, -10, -9 and 0, 1, 2 and 7, 8, 9 (total dose = 540 µg/kg) • (n = 37): 60 µg/kg per day in 12 doses on days -11, -10, -9 and 0, 1, 2 and 7, 8, 9 and 14, 15, 16 (total dose = 720 µg/kg) <p>Group B: placebo with matching schedule to either the 6, 9 or 12 dose regimen</p> <p>Mode of administration not described but presumably IV as in other KGF studies</p> <p>Compliance: Group A: 20 did not receive all study doses (17 of these were replaced to allow a full assessment of safety); Group B: 2 did not receive all study doses (1 replaced)</p> <p>Duration of treatment: varied from 13 days (6 doses) to 27 days (12 doses) - see above</p>

Outcomes	<ul style="list-style-type: none">• Oral mucositis: WHO 0 to 4 scale (measured 3 times per week during hospitalisation by designated observers, maximum score reported)• Adverse effects (assessed daily during study period using WHO and NCI-CTC toxicities scale)• Incidence and severity of acute GVHD (not an outcome of this review)• Overall survival (not an outcome of this review)• Incidence of transplantation-related toxicity (not an outcome of this review)• Time to marrow engraftment (not an outcome of this review)	
Notes	<p>Sample size calculation: not reported</p> <p>Funding: government grants from NIH and FDA, and also supported by Amgen (pharmaceutical industry)</p> <p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: the data for incidence of mucositis were not reported separately for each dose and therefore it was not possible to include head-to-head comparisons of different dosages in this review; the data for incidence of mucositis were presented in subgroups of those that did or did not receive the final methotrexate infusion on day 11 but we used the overall data in our meta-analyses (the study authors report that there was no difference between these subgroups)</p> <p>Other information of note: the study authors report a greater decrease in incidence of grade 3 to 4 (severe) oral mucositis due to palifermin in the Minnesota participants (who received a more mucotoxic conditioning regimen) than in the Michigan participants</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients...were randomly assigned." .. Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "patients...were randomly assigned." .. Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" Comment: it is not clear who was blinded. There are subjective elements to the assessment of oral mucositis using this scale, requiring the patient's assessment of pain/

Blazar 2006 (Continued)

		soreness and their ability to swallow but, as the participants were unaware of their group allocation, the assessment of oral mucositis can be considered to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Data for all patients randomly assigned and who received a transplant were used in all other analyses (intent-to-treat)" Comment: although 18 participants (Group A: 17; Group B: 1) were replaced to allow a full assessment of safety, it seems that the originally randomised participants were included in the analyses Overall attrition was 4% (Group A: 6%; Group B: 0%) for the oral mucositis incidence outcome. The reasons were unclear but this proportion of attrition is unlikely to have biased the results
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Blijlevens 2013

Methods	<p>Trial design: parallel (3 arms)</p> <p>Location: Europe (Italy, France, the Netherlands, Ireland, Germany, UK, Denmark, Austria, Switzerland, Czech Republic, Sweden, Hungary, Belgium, Finland)</p> <p>Number of centres: 39</p> <p>Study duration: December 2006 to February 2009</p> <p>Trials registry number: NCT00434161</p>
Participants	<p>Inclusion criteria: aged between 18 and 70 years; due to receive high-dose melphalan; ECOG score of 0 to 2 (or 3, if reason was due to multiple myeloma); at least 2×10^9 CD34+ cells per kg; corrected carbon monoxide diffusing capacity 50% or higher of predicted; absolute neutrophil count at least 1.5×10^9 /L and platelets at least 100×10^9 /L; total bilirubin 2 mg/dL or lower; aspartate aminotransferase and/or alanine aminotransferase 4 x institutional upper limit of normal or lower</p> <p>Exclusion criteria: not reported</p> <p>Cancer type: multiple myeloma</p> <p>Cancer treatment: 1-day administration of high-dose melphalan (200 mg/m²) on day -2, followed by auto-SCT on day 0</p> <p>Age at baseline (years): Group A: median 55 (range 32 to 69); Group B: median 58 (range 40 to 68); Group C: median 58 (range 41 to 68)</p> <p>Gender: Group A: 54% male; Group B: 55% male; Group C: 58% male</p> <p>Number randomised: 281 (Group A: 109; Group B: 115; Group C: 57)</p> <p>Number evaluated: 281 (Group A: 109; Group B: 115; Group C: 57)</p>

Interventions	<p>Comparison: KGF versus placebo</p> <p>Group A: KGF (60 µg/kg) daily IV on days -6, -5, and -4, then placebo on days 0 (the day of auto-SCT), 1, and 2 (total dose = 180 µg/kg)</p> <p>Group B: KGF (60 µg/kg) daily IV on days -6, -5, -4, 0, 1, and 2 (total dose = 360 µg/kg)</p> <p>Group C: placebo daily IV on days -6, -5, -4, 0, 1, and 2</p> <p>Compliance: Group A: 8% discontinued; Group B: 12% discontinued; Group C: 4% discontinued; (point of discontinuation or number of treatments not stated for any group)</p> <p>Duration of treatment: 6 treatment days (over 9 days)</p>	
Outcomes	<ul style="list-style-type: none">• Oral mucositis: WHO 0 to 4 scale (assessed daily by nurses and physicians from day -2 to day 32, maximum score reported) (duration of grade 2 to 4 and 3 to 4 oral mucositis also measured but not outcomes of this review)• Oral pain: OMDQ 5-point scale for mouth and throat soreness (higher = worse pain) (assessed daily by participants from day -2 to day 32, data reported as AUC, not used)• Quality of life: EQ-5D 0 (worst imaginable health) to 10 (best imaginable health) scale, incorporating mobility, self-care, usual activities, pain/discomfort and anxiety/depression (assessed daily by participants from day -2 to day 32, mean reported only at day 7 and with no SD, no usable data)• Normalcy of diet (measured as incidence of TPN) (duration of TPN also measured but not used for analysis in review)• Adverse events (NCI-CTC version 3.0 toxicity scale)• Number of days in hospital• Number of days of treatment with opioid analgesics (incidence of opioid analgesic use also measured and reported but not an outcome of this review)• Febrile neutropenia (not an outcome of this review)• Significant infections (not an outcome of this review)• Anti-infective (IV) drug use (not an outcome of this review)• Blood product use (not an outcome of this review)• Nonopioid analgesic use (not an outcome of this review)	
Notes	<p>Sample size calculation: 275 participants required at 95% power and 5% significance to detect an odds ratio of at least 3.5 between placebo and KGF in grade 2 to 4 oral mucositis</p> <p>Funding: sponsored by Swedish Orphan Biovitrum (pharmaceutical industry); KGF and placebo manufactured and packaged by Amgen (pharmaceutical industry)</p> <p>Declarations/conflicts of interest: 2 authors were employees of the sponsors; the remaining authors declared no competing financial interests</p> <p>Data handling by review authors: we combined the 2 KGF groups to make a single pairwise comparison against placebo; we also made a separate comparison of the 2 KGF regimens</p> <p>Other information of note: not reported</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by using an interactive-voice-response-system before planned admission" Comment: large multicentre trial using high-tech randomisation method - likely to be done properly
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed by using an interactive-voice-response-system before planned admission" Comment: large multicentre trial using high-tech randomisation method - likely to be done properly
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" and "Study drug...packaged...in identical vials" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" Comment: it is not clear who was blinded. There are subjective elements to the assessment of lower grades of oral mucositis using the WHO scale, requiring the patient's assessment of pain/soreness and their ability to swallow. Higher grades have more objective elements so may not be affected by potential lack of blinding of the assessor. This would be the same for other subjective and objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately (although quality of life reported with no SD or P values, this does not affect the risk of bias judgement for other outcomes)
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Australia</p> <p>Number of centres: 23</p> <p>Study duration: recruitment from September 2006 to April 2010</p> <p>Trials registry number: ACTRN012605000095662 (mentioned in trial report)</p>
Participants	<p>Inclusion criteria: aged 15 to 60 years with newly diagnosed and previously untreated (except for hydroxycarbamide for high presenting white blood cell count) acute myeloid leukaemia - all subtypes except t(15;17) or variants, or core-binding factor AML (t(8;21) or inv(16) or variants); ECOG score of 0 to 3; no history of cancer (other than basal cell skin cancer or carcinoma of the cervix in situ, or other localised cancer treated by surgical excision only more than 5 years earlier without evidence of recurrence in the intervening period)</p> <p>Exclusion criteria: not reported</p> <p>Cancer type: acute myeloid leukaemia</p> <p>Cancer treatment: induction chemotherapy consisting of: idarubicin 9 mg/m² daily IV infusion on days 1 to 3; etoposide 75 mg/m² daily IV infusion on days 1 to 7; cytarabine 3 g/m² 12-hourly IV infusion on days 1, 3, 5, and 7</p> <p>All participants received G-CSF (pegfilgrastim) 6 mg subcutaneously on day 8</p> <p>Age at baseline (years): Group A: mean 46 (SD 12; range 17 to 60); Group B: mean 44 (SD 12; range 16 to 60)</p> <p>Gender: Group A: 61% male; Group B: 67% male</p> <p>Number randomised: 160 (Group A: 79; Group B: 81)</p> <p>Number evaluated: 151 (Group A: 73; Group B: 78)</p>
Interventions	<p>Comparison: KGF (palifermin) versus placebo</p> <p>Group A: KGF (60 µg/kg) daily IV on days -3, -2, -1 prior to chemotherapy and for 3 days after completion of chemotherapy (total dose = 360 µg/kg)</p> <p>Group B: same schedule with placebo</p> <p>Compliance: received all 3 pre-chemotherapy doses: Group A: 97%; Group B: 100%; received all 3 post-chemotherapy doses: Group A: 95%; Group B: 96%</p> <p>Duration of treatment: 6 treatment days (over 14 days)</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale (assessed daily by investigators and specifically trained site personnel from the first day of chemotherapy and until the earlier of the date of discharge or day 28 after the start of chemotherapy, maximum score reported) (duration of grade 3 to 4 oral mucositis also measured but not an outcome of this review) • Adverse events (NCI-CTC version 2.0 toxicity scale) • Incidence of severe gastrointestinal toxicities related to the induction chemotherapy (not an outcome of this review) • Complete response to chemotherapy (not an outcome of this review)
Notes	<p>Sample size calculation: 128 per group required to detect a reduction in grade 3 to 4 mucositis from 22% to 10% at 70% power and 5% significance</p> <p>Funding: "This study was funded in part from Project Grant 302133 from the National Health and Medical Research Council of Australia" (government); KGF and placebo provided by Amgen (pharmaceutical industry)</p> <p>Declarations/conflicts of interest: "The authors have no conflicts of interest to declare"</p>

Data handling by review authors: N/A Other information of note: not reported		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized 1:1 using a block randomization technique and stratification by participating centre to receive placebo or palifermin" Comment: large multicentre trial using block randomisation and stratification - likely to be done properly
Allocation concealment (selection bias)	Unclear risk	Quote: "Eligible patients were randomized 1:1 using a block randomization technique and stratification by participating centre to receive placebo or palifermin" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo-controlled" and "Both investigators and patients were blinded to the randomization outcome" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "placebo-controlled" and "Both investigators and patients were blinded to the randomization outcome" Comment: investigators assessed oral mucositis, which would have partly relied on patient's assessment of pain/soreness and their ability to swallow; both investigators and patients were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition was 6% (Group A: 8%; Group B: 4%) for the oral mucositis incidence outcome. The reasons were similar between groups and this proportion of attrition is unlikely to have biased the results
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Australia, Canada and USA</p> <p>Number of centres: 22</p> <p>Study duration: September 1999 to May 2001</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: adults with newly diagnosed stage III/IVa or IVb squamous carcinoma of the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx (or with unknown primary and extensive neck disease) undergoing CRT intended to be curative; Karnofsky performance score of 60 or higher; haemoglobin 10 g/dL or higher; white blood cell count 3.5×10^9 /L or higher or absolute neutrophil count 1.5×10^9 /L or higher; platelet count 100×10^9 /L or higher; serum bilirubin 1.5 mg/dL or lower; serum creatinine lower than 2.0 mg/dL (plus a 24-hour urinary creatinine clearance 50 mL/min in those aged 60 years or older)</p> <p>Exclusion criteria: previous RT to the head and neck; previous surgery for the primary tumour (not including biopsy); previous CT; allergy to Escherichia coli-derived products; participation in any other investigational study within the 30 days prior to this study; refusal to use adequate contraception during the study; pregnant or breastfeeding</p> <p>Cancer type: head and neck: oral (Group A: 12%; Group B: 6%); oropharynx/nasopharynx (Group A: 61%; Group B: 66%); hypopharynx/larynx (Group A: 27%; Group B: 28%)</p> <p>Cancer treatment:</p> <ul style="list-style-type: none"> • Radiotherapy: standard (once daily 2-Gy fractions, 5 days per week; total 70 Gy over 7 weeks) or hyperfractionated (twice daily 1.25-Gy fractions with 6-hour interval, 5 days per week with an 8 to 9 day break after 3 weeks; total 72 Gy over 6.5 weeks) • Chemotherapy: cisplatin (20 mg/m²/day) as IV bolus injection and 5FU (1000 mg/m²/day) as continuous infusion on the first 4 days of the first and fifth weeks of radiotherapy <p>Age at baseline (years): Group A: mean 54 (SD 10; range 25 to 80); Group B: mean 56 (SD 10; range 42 to 75)</p> <p>Gender: Group A: 82% male; Group B: 84% male</p> <p>Number randomised: 101 (Group A: 69; Group B: 32)</p> <p>Number evaluated: 97 (Group A: 65; Group B: 32)</p>
Interventions	<p>Comparison: KGF (palifermin) versus placebo</p> <p>Group A: KGF 60 µg/kg once weekly by IV bolus injection starting on the Friday before CRT began (on the following Monday), then each Friday after completion of RT for 7 weeks, and 2 more doses after completion of CRT i.e. 10 doses in total (total dose = 600 µg/kg)</p> <p>Group B: same schedule with matching placebo</p> <p>Compliance: 99 participants (Group A: 67; Group B: 32) received at least 1 dose of their allocated intervention; 69 participants completed the full course (Group A: 47; Group B: 22); mean number of doses (Group A: 8.4; Group B: 9.1)</p> <p>Duration of treatment: 9 weeks (10 doses)</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: NCI-CTC (2.0) 0 to 4 scale (measured weekly by a radiation oncologist for the first 12 weeks, reported as incidence of grade 2 to 4 i.e. moderate to severe, and grade 3 to 4 i.e. severe) (duration, time to onset, and cumulative radiotherapy dose at onset of grade 2+ and 3+ oral mucositis also measured but not outcomes of this review)

	<ul style="list-style-type: none">• Interruptions to cancer treatment (unscheduled radiotherapy breaks: reported as any breaks and breaks longer than 4 days)• Normalcy of diet (measured as incidence of supplemental nutrition by a gastrostomy tube)• Adverse effects (reports collected throughout the 20-week study)• Opioid analgesic use (reported as incidence; number of days of treatment with opioid analgesics is an outcome of this review and therefore we did not use these data)• Dysphagia (not an outcome of this review)• Xerostomia (not an outcome of this review)• Antibiotic use (not an outcome of this review)• Tumour response rate (not an outcome of this review)• Progression-free and overall survival (assessed in a longer-term follow-up study) (not an outcome of this review)	
Notes	<p>Sample size calculation: based on a previous study, 99 participants required to detect a 30% difference in the duration of grade 2 or higher oral mucositis with 80% power provided that the mean duration in the placebo arm was 56 days</p> <p>Funding: “Supported by Amgen Inc” (pharmaceutical industry)</p> <p>Declarations/conflicts of interest: multiple and involving: employment or leadership positions with the funders (Amgen); consultant or advisory roles with the funders and other pharmaceutical companies; stock ownership with the funders; honoraria from the funders and other pharmaceutical companies; research funding from the funders and other pharmaceutical companies</p> <p>Data handling by review authors: the data for incidence of mucositis were presented in subgroups of those that received standard or hyperfractionated RT but we used the overall data in our meta-analyses; for the interruptions to radiotherapy outcome, we used the data for breaks longer than 4 days as these could be pooled with other studies in this comparison</p> <p>Other information of note: the study authors report a greater decrease in incidence due to palifermin in the hyperfractionated subgroup than in the standard subgroup (see figure 3A in the study report)</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Patients were randomly assigned..” Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: “Patients were randomly assigned..” Comment: insufficient information to determine whether or not the random sequence was adequately concealed

Brizel 2008 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double blinded” and “Palifermin. ..or matching placebo was administered by intravenous bolus” Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double blinded” and “Palifermin. ..or matching placebo was administered by intravenous bolus” Comment: it is not clear who was blinded. There are subjective elements to the assessment of oral mucositis using this scale, requiring the patient’s assessment of pain/soreness and their ability to swallow but, as the participants were unaware of their group allocation, the assessment of oral mucositis can be considered to be blinded. The other outcomes are objective and therefore unlikely to be affected by any potential lack of blinding of the outcome assessor(s)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition was 4% (Group A: 6%; Group B: 0%) for the oral mucositis incidence outcome. The reasons were unclear but this proportion of attrition is unlikely to have biased the results
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Cartee 1995

Methods	Trial design: parallel (5 arms) dose-ranging study Location: Duke University Medical Centre, Durham, North Carolina, USA Number of centres: 1 Study duration: not reported Trials registry number: none/unknown
Participants	Inclusion criteria: premenopausal or perimenopausal patients with histologically confirmed metastatic breast cancer who had chemotherapy for inoperable or metastatic disease; performance status of 0 or 1 (CALGB criteria) Exclusion criteria: metastatic disease involving the central nervous system; pregnant Cancer type: stage IV breast Cancer treatment: AFM regimen (21-day cycle): 5FU (500 mg/m ² /day) continuous infusion on days 1 to 5; adriamycin (25 mg/m ²) IV bolus on days 3 to 5; methotrexate

	<p>(250 mg/m²) IV on day 15 (if oral mucositis less than grade 3)</p> <p>All participants received G-CSF (filgrastim) subcutaneously (5 µg/kg/day) on days 7 to 13 and from day 16 until resolution of neutropenia</p> <p>Age at baseline (years): mean 44 (not reported by group)</p> <p>Gender: 49 female; 1 male (not reported by group)</p> <p>Number randomised: 50 (not reported by group)</p> <p>Number evaluated: 45 (Group A: 36; Group B: 9)</p>
Interventions	<p>Comparison: GM-CSF (molgramostim) versus placebo</p> <p>Group A: GM-CSF</p> <ul style="list-style-type: none"> • (n = 9 analysed): 15 mL of mouthwash (0.01 µg/mL) gently swirled in the mouth for 2 minutes before expectorating it; 4 times daily (after mealtimes, even if a meal was not eaten, and at bedtime) after routine oral care procedures; no eating/drinking for 15 minutes after using mouthwash; beginning within 24 hours of the start of 5FU and continued for the 21-day AFM cycle (total dose = 12.6 µg) • (n = 9 analysed): same schedule with 0.1 µg/mL mouthwash (total dose = 126 µg) • (n = 9 analysed): same schedule with 1 µg/mL mouthwash (total dose = 1260 µg) • (n = 9 analysed): same schedule with 10 µg/mL mouthwash (total dose = 12,600 µg) <p>Group B: (n = 9 analysed) same schedule with matching placebo mouthwash</p> <p>Compliance: (not reported by group) mouthwash therapy was discontinued if the participant experienced oral mucositis of grade 3 or above; 30 participants took at least 80% of their prescribed doses; 11 participants discontinued mouthwash therapy within 3 days prior to day 15; 4 participants discontinued mouthwash therapy between day 15 and day 21</p> <p>Duration of treatment: 21 days (first treatment cycle of AFM)</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: CALGB 0 to 4 scale (measured on days 1 to 5, 8 to 10, 15 and 22, reported as incidence of grade 3 to 4 i.e. severe) (duration of grade 3 to 4 oral mucositis also measured but not an outcome of this review) • Adverse effects (assessed during study period) • Blood measurements (platelet, WBC, granulocyte, lymphocyte) (not an outcome of this review) • Myelosuppression (not an outcome of this review) • GM-CSF plasma concentrations (not an outcome of this review)
Notes	<p>Sample size calculation: this was done but the numbers required are not reported</p> <p>Funding: "...supported in part by National Cancer Institute (Bethesda, MD) grant number PO1-47741-A4"</p> <p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: we combined the 4 GM-CSF groups to make a single pairwise comparison against placebo and, in order to make a head-to-head comparison of doses, we grouped the 2 lower doses (0.01 µg/mL and 0.1 µg/mL) together and grouped the 2 higher doses (1 µg/mL and 10 µg/mL) together to make pairwise groups for comparison</p> <p>Other information of note: not reported</p>
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized by the Duke Cancer Center Protocol Office according to a block randomization scheme and assigned a unique identifier number which designated the GM-CSF dose level to be received" Comment: method of sequence generation not fully described but was done by a dedicated specialist centre so was probably done adequately
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized by the Duke Cancer Center Protocol Office" and "The patient supply of mouthwash was labelled to correspond with the assigned identifier number and dispensed by the Pharmacy. The patient assignment information was maintained by the Pharmacy" Comment: the entire randomisation process was performed by third party so the random sequence is unlikely to have been manipulated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" and "The patient assignment information was maintained by the Pharmacy" Comment: it is not clear who was blinded. There are subjective elements to the assessment of oral mucositis using this scale, requiring the patient's assessment of pain/soreness and their ability to swallow but, as the participants were unaware of their group allocation, the assessment of oral mucositis can be considered to be blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall attrition was 10%. Reasons for attrition fully reported. If all participants would have developed severe oral mucositis or dropped out due to severe oral mucositis and were all from 1 particular group, this would have biased the results. However, attrition was not reported by group, so it is unclear

Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Cesaro 2013

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Italy</p> <p>Number of centres: 4</p> <p>Study duration: May 2007 to June 2011</p> <p>Trials registry number: EudraCT 2007-001430-14 (mentioned in trial report)</p>
Participants	<p>Inclusion criteria: aged 0 to 17 years with leukaemia, lymphoma or solid tumour; due to receive a first autologous PBSCT</p> <p>Exclusion criteria: not reported</p> <p>Cancer type: leukaemia/lymphoma (Group A: 22%; Group B: 17%); solid (Group A: 78%; Group B: 83%) (neuroblastoma, Ewing sarcoma/peripheral neuroectodermal tumour, medulloblastoma, Wilms tumour, central nervous system tumour)</p> <p>Cancer treatment: all participants had autologous PBSCT on day 0 but differed in conditioning regimen as follows:</p> <ul style="list-style-type: none"> • Chemotherapy: multiple regimens involving 1 to 4 chemotherapy drugs; the most common regimen was busulfan 16 mg/kg with melphalan 140 mg/m² (Group A: 53%; Group B: 37%) • Radiotherapy: only 4 participants (2 in each arm) had TBI 12 Gy to 14.4 Gy prior to their chemotherapy <p>Age at baseline (years): Group A: median 11.1 (range 1.7 to 17.4); Group B: median 11.9 (range 1.6 to 17.2)</p> <p>Gender: Group A: 66% male; Group B: 59% male</p> <p>Number randomised: 61 (Group A: 32; Group B: 29)</p> <p>Number evaluated: 61 (Group A: 32; Group B: 29)</p>
Interventions	<p>Comparison: G-CSF (pegfilgrastim) versus G-CSF (filgrastim)</p> <p>Group A: pegfilgrastim single dose (100 µg/kg; maximum 6 mg) injected on day 3</p> <p>Group B: filgrastim (5 µg/kg per day; maximum 300 µg per day) injected by 9 or more doses starting on day 3 (total dose = at least 45 µg/kg)</p> <p>Mode of administration not described but presumably subcutaneously as in other G-CSF studies</p> <p>Compliance: all participants received their allocated intervention with no discontinuations</p> <p>Duration of treatment: Group A: 1 day; Group B: 9 or more days</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale (reported as incidence of any mucositis and grade 2 to 4 i.e. moderate to severe) (duration of any mucositis also measured but not an outcome of this review) • Normalcy of diet (measured as incidence of TPN) (duration of TPN also measured but not used for analysis in review)

	<ul style="list-style-type: none">● Adverse events● Number of days in hospital (reported as median and range, unable to use data)● Polymorphonuclear cell recovery (not an outcome of this review)● Time to platelet engraftment (not an outcome of this review)● Incidence of febrile neutropenia and proven infection (not an outcome of this review)● Duration of IV antibiotics (not an outcome of this review)● Survival (not an outcome of this review)	
Notes	<p>Sample size calculation: based on the noninferiority of pegfilgrastim versus filgrastim in speeding the recovery of polymorphonuclear cells</p> <p>Funding: “The authors have no support or funding to report”</p> <p>Declarations/conflicts of interest: “The authors have declared that no competing interests exist”</p> <p>Data handling by review authors: N/A</p> <p>Other information of note: G-CSF administration only began after the chemotherapy and PBSCT were completed, by which point oral mucositis may have already begun to develop</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “A computer-generated randomisation list was drawn up at Data Office Centre of AIEOP in Bologna, Italy, by a statistician not involved in patient management” Comment: adequate method used
Allocation concealment (selection bias)	Low risk	Quote: “The list was stored by sequentially numbered sealed envelopes that was concealed to investigators until the completion of recruitment. The local investigator ...assigned each eligible patient to randomization list by phoning to AIEOP Data Office Centre” Comment: ideal method of concealment used
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment regimens were different so blinding not possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It would be possible to blind the outcome assessor for oral mucositis, but it was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses

Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Chi 1995

Methods	<p>Trial design: cross-over (2 arms)</p> <p>Location: Cancer Centre and Department of Otolaryngology, Veterans General Hospital, Taiwan, Republic of China</p> <p>Number of centres: 1</p> <p>Study duration: not reported</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: diagnosed stage IV SCC of head and neck, previously untreated or locally recurrent after previous surgery or radiotherapy or both; ECOG score of 2 or above; adequate bone marrow, liver and renal function</p> <p>Exclusion criteria: concurrent medical illness; local radiotherapy to oropharynx region in the previous 3 months</p> <p>Cancer type: head and neck: nasopharyngeal (Group A: 44%; Group B: 27%); tongue (Group A: 22%; Group B: 36%); hypopharynx (Group A: 11%; Group B: 18%); buccal (Group A: 11%; Group B: 9%); tonsillar (Group A: 11%; Group B: 9%)</p> <p>Cancer treatment: PFL regimen (21-day cycle): cisplatin (20 mg/m²/day), 5FU (800 mg/m²/day) and leucovorin (90 mg/m²/day) IV for days 1 to 4; cycle repeated every 3 weeks (study consisted of 2 cycles)</p> <p>Age at baseline (years): Group A: median 44 (range 36 to 62); Group B: median 49 (range 40 to 66)</p> <p>Gender: Group A: 89% male; Group B: 91% male</p> <p>Number randomised: 20 (Group A: 9; Group B: 11) - figures for first cycle</p> <p>Number evaluated: 20 (Group A: 9; Group B: 11)</p>
Interventions	<p>Comparison: GM-CSF versus no treatment</p> <p>Group A: GM-CSF (4 µg/kg) subcutaneously from day 5 to 14 (total dose = 40 µg)</p> <p>Group B: no treatment</p> <p>Compliance: not reported</p> <p>Duration of treatment: 10 days (days 5 to 14 of 21-day cycle)</p>
Outcomes	<ul style="list-style-type: none"> Oral mucositis: RTOG 0 to 4 scale (measured on days 5 to 21 by both physician's objective gross score and participant's subjective functional score, reported as area under the curve and also in the text as incidence of severe gross mucositis i.e. grade 3 to 4) (duration of grade 2 to 4 and 3 to 4 oral mucositis also measured but not an outcome of this review) Adverse effects (assessed across both cycles)
Notes	<p>Sample size calculation: not reported</p> <p>Funding: "...supported in part by Department of Health, Taiwan, Republic of China, research grant no. DOH 83-HR-202" and "GM-CSF (supplied by Schering Plough Corp, Kenilworth, NJ)" (pharmaceutical industry)</p>

	<p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: as stated in the methods section, we would only include first-period data from cross-over studies due to potential for period effects (which were reported in this study). The only usable data in this study were reported in the text as incidence of severe gross mucositis for the first cycle</p> <p>Other information of note: the authors report a significant period effect of GM-CSF ($P < 0.01$), whereby the benefits continued into the second cycle</p> <p>GM-CSF administration only began after the 4-day chemotherapy was completed, by which point oral mucositis may have already begun to develop</p>
--	---

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomized to receive GM-CSF or no therapy" Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized to receive GM-CSF or no therapy" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comparison with no treatment so blinding not possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It would be possible to blind the outcome assessor, as the data we used were assessed by a physician using an objective scale. However, it was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants appear to be included in the analyses
Selective reporting (reporting bias)	Low risk	Although most of the data were not usable in this review, this does not seem to be due to selective reporting
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: USA</p> <p>Number of centres: 14</p> <p>Study duration: recruitment from May 1988 to November 1989</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: newly diagnosed small-cell lung cancer meeting standard criteria for end-organ function; ECOG score of 0 to 2</p> <p>Exclusion criteria: previous radiotherapy; other serious medical illnesses precluding participation</p> <p>Cancer type: small-cell lung cancer</p> <p>Cancer treatment: CAE regimen (21-day cycle): cyclophosphamide (1000 mg/m²) and doxorubicin (50 mg/m²) on day 1; etoposide (120 mg/m²) on days 1 to 3; all by IV; repeated for up to 6 cycles</p> <p>Age at baseline (years): Group A: mean 61 (SD 10; range 31 to 78); Group B: mean 62 (SD 8; range 31 to 80)</p> <p>Gender: Group A: 65% male; Group B: 63% male</p> <p>Number randomised: 211 (Group A: 101; Group B: 110)</p> <p>Number evaluated: 195 (Group A: 93; Group B: 102) - figures for first cycle</p>
Interventions	<p>Comparison: G-CSF (r-metHuG-CSF) (filgrastim) versus placebo</p> <p>Group A: G-CSF (230 µg/m²) self-administered subcutaneously on days 4 to 17 (total dose = 3220 µg/m²)</p> <p>Group B: as above but with placebo</p> <p>G-CSF stopped if postnadir neutrophil count exceeded 10 x 10⁹ /L after day 12; participants kept receiving their allocated intervention until they experienced fever with neutropenia, then they received unblinded G-CSF (230 µg/m²) in subsequent cycles; participants in the G-CSF group who experienced fever with neutropenia were allowed 25% reduction in chemotherapy dosages in subsequent cycles</p> <p>Compliance: not reported</p> <p>Duration of treatment: 14 days during a 21-day cycle</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale (measured weekly, reported as incidence of any mucositis) (duration and time to onset of oral mucositis also measured but not an outcome of this review) • Adverse effects (assessed over the 6 cycles) • Number of days in hospital (reported graphically in secondary trial report with no SD or P value, no usable data) • Incidence, duration and severity of fever with neutropenia (not an outcome of this review) • Incidence and duration of antibiotic use (not an outcome of this review)
Notes	<p>Sample size calculation: based on a difference of 20% in the incidence of fever with neutropenia over the 6 cycles</p> <p>Funding: "The study was designed, coordinated, and analyzed in conjunction with Amgen, the supplier of the G-CSF"</p> <p>Declarations/conflicts of interest: not reported but some authors were employed by Amgen (pharmaceutical industry)</p>

<p>Data handling by review authors: for oral mucositis, we only used the data from the first cycle due to the reasons listed above (under 'Interventions')</p> <p>Other information of note: G-CSF administration only began after the 3-day chemotherapy was completed, by which point oral mucositis may have already begun to develop</p>		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to chemotherapy followed by study drug (either placebo or G-CSF)" Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to chemotherapy followed by study drug (either placebo or G-CSF)" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo was supplied in matching vials for double blinding" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Placebo was supplied in matching vials for double blinding" Comment: it is not clear who was blinded. There are subjective elements to the assessment of oral mucositis using this scale, requiring the patient's assessment of pain/soreness and their ability to swallow but, as the participants were unaware of their group allocation, the assessment of oral mucositis can be considered to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition was 8% (Group A: 8%; Group B: 7%) for the oral mucositis incidence outcome. The reasons were reported and similar between groups, and this proportion of attrition is unlikely to have biased the results
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately

Other bias	Low risk	No other sources of bias are apparent
------------	----------	---------------------------------------

Dazzi 2003

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Ravenna, Italy</p> <p>Number of centres: 1</p> <p>Study duration: recruitment from July 1997 to February 2002</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: 14 years of age or older; hospitalised for high-dose chemotherapy with autologous PBST</p> <p>Exclusion criteria: not reported</p> <p>Cancer type: breast (Group A: 17.5%; Group B: 27.5%); Ewing's sarcoma (Group A: 41.5%; Group B: 28.5%); osteosarcoma (Group A: 13%; Group B: 14%); NHL (Group A: 15%; Group B: 11.5%); germ cell tumours (Group A: 11%; Group B: 16%); small-cell lung (Group A: 2%; Group B: 0%); soft tissue sarcoma (Group A: 0%; Group B: 2.5%)</p> <p>Cancer treatment: high-dose chemotherapy with autologous PBST; chemotherapy regimens were categorised into high risk and low risk and this was used as a stratification factor for randomisation, therefore high- and low-risk participants were equally distributed across groups</p> <p>All participants received subcutaneous G-CSF (300 µg/day) until haematopoietic reconstitution</p> <p>Age at baseline (years): Group A: median 29 (range 15 to 57); Group B: median 29 (range 17 to 61)</p> <p>Gender: Group A: 59% male; Group B: 55% male</p> <p>Number randomised: 90 (Group A: 46; Group B: 44)</p> <p>Number evaluated: 90 (Group A: 46; Group B: 44)</p>
Interventions	<p>Comparison: GM-CSF versus placebo</p> <p>Group A: GM-CSF mouthwash 150 µg/day in 100 cm³ of sterile water taken in 4 doses per day; mouthrinsing performed for 1 minute each time; treatment started on the day after the completion of chemotherapy and continued until bone marrow recovery (absolute neutrophil count > 500/mm³) or resolution of mucositis if still persistent after bone marrow recovery (total dose = variable)</p> <p>Group B: as above but with placebo (sterile water)</p> <p>All participants received 0.2% oral chlorhexidine and amphotericin B</p> <p>Compliance: all but 7 participants regularly completed mouthwashes: 1 participant in the placebo group had none due to persistent vomiting; 6 (4 in placebo group and 2 in GM-CSF group) started treatment but interrupted it early due to nausea and vomiting</p> <p>Duration of treatment: variable and dependent on bone marrow recovery/resolution of mucositis</p>

Outcomes	<ul style="list-style-type: none">• Oral mucositis: NCI-CTC 0 to 4 scale (measured daily by the physicians, reported as incidence of mucositis and incidence of grade 3 to 4 i.e. severe) (duration of grade 3 to 4 oral mucositis also measured but not an outcome of this review)• Oral pain: 0 to 10 VAS (self-evaluated daily, reported as mean worst score experienced)• Number of days of treatment with opioid analgesics (also reported as incidence; we did not use these data)	
Notes	<p>Sample size calculation: 90 participants required to detect 25% minimal difference in the rate of severe mucositis at 90% power and 5% significance</p> <p>Funding: no external funding (from correspondence with authors)</p> <p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: the data for incidence of mucositis were presented in subgroups of those at low or high risk of mucositis but we used the overall data in our meta-analyses</p> <p>Other information of note: there does not appear to be any difference in risk of any or severe mucositis between the low- and high-risk subgroups</p> <p>GM-CSF administration only began after the chemotherapy was completed, by which point oral mucositis may have already begun to develop</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote from correspondence with authors: "The randomization list was centralized"</p> <p>Comment: centralised randomisation method - likely to be done properly</p>
Allocation concealment (selection bias)	Low risk	<p>Quote from correspondence with authors: "The randomization list was centralized"</p> <p>Comment: centralised randomisation method - likely to be done properly</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "double-blind, randomized, placebo-controlled study" and "The color, odor, texture and taste of both solutions were virtually identical"</p> <p>Comment: the use of a placebo should have ensured that blinding was successful</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "double-blind, randomized, placebo-controlled study"</p> <p>Comment: it is not clear who was blinded. There are subjective elements to the assess-</p>

		ment of oral mucositis using this scale, requiring the patient's assessment of pain/soreness and their ability to swallow but, as the participants were unaware of their group allocation, the assessment of oral mucositis can be considered to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Fink 2011

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Department of Hematology and Oncology, University Hospital Freiburg, Germany</p> <p>Number of centres: 1</p> <p>Study duration: March 2006 to December 2010</p> <p>Trials registry number: EudraCT 2008-001833-87; DRKS00000043</p>
Participants	<p>Inclusion criteria: adults aged 18 to 75 years with either: high-grade non-Hodgkin's lymphoma with high-risk syndrome (> 2 risk factors according to age-adapted IPI = international prognostic index) in the first complete remission; Hodgkin's lymphoma in the first recurrence; recurrence of follicular lymphoma; primary therapy of a coat-cell lymphoma (MCL) in stage II-IV; due to receive BEAM chemotherapy followed by autologous PBSCT; Karnofsky performance score more than 60%; life expectancy more than 3 months</p> <p>Exclusion criteria: previous therapy using palifermin; severe concomitant diseases with organ failure; pregnancy, lactation, positive pregnancy test; hypersensitivity to 1 of the trial drugs; severe psychiatric illness; HIV disease or immunologic deficiency; known central nervous system involvement</p> <p>Cancer type: haematologic: diffuse large-cell lymphoma (Group A: 33%; Group B: 42%); B-cell type acute lymphocytic leukaemia (Group A: 10%; Group B: 6%); T-cell non-Hodgkin's lymphoma (Group A: 13%; Group B: 11%); follicular/mantle cell lymphoma (Group A: 27%; Group B: 28%); Hodgkin's lymphoma (Group A: 17%; Group B: 14%)</p> <p>Cancer treatment: prior to receiving autologous PBSCT on day 0, participants received BEAM conditioning regimen from day -8 to -2: carmustine (BCNU) 300 mg/m²; etoposide 800 mg/m²; cytosine arabinoside 1600 mg/m²; melphalan 140 mg/m²</p> <p>Age at baseline (years): (ITT population) Group A: median 50 (range 22 to 71); Group B: median 55 (range 22 to 73)</p> <p>Gender: (ITT population) Group A: 57% male; Group B: 61% male</p> <p>Number randomised: 73 (Group A: 37; Group B: 36)</p> <p>Number evaluated: ITT: 66 (Group A: 30; Group B: 36); PP: 54 (Group A: 22; Group B: 32)</p>

Interventions	Comparison: KGF (palifermin) plus best supportive care versus best supportive care alone Group A: KGF (60 µg/kg) by IV daily for 3 days (days -10, -9, -8) prior to conditioning regimen and autologous PBSCT and then for 3 days after (days 0, 1, 2) (total dose = 360 µg/kg) Group B: best supportive care (“effective oral hygiene like teeth brushing, oral rinsing”) beginning on day -8 (the day of hospital admission for BEAM conditioning) Compliance: Group A: 7/37 withdrew before therapy started, 3/37 had a different conditioning regimen to that specified in the study protocol (unclear if they still received KGF), 5/37 either had no KGF or did not receive all doses; Group B: 4/36 had a different conditioning regimen to that specified in the study protocol (unclear if they still received control intervention) Duration of treatment: 6 treatment days (over 13 days)	
Outcomes	<ul style="list-style-type: none">• Oral mucositis: WHO 0 to 4 scale (measured daily during hospital stay by trained nurses, study assistant, or treating physician, maximum score reported) (duration of oral mucositis also measured but not an outcome of this review)• Normalcy of diet (measured as incidence of TPN)• Adverse events• Number of days in hospital (medians reported, unable to use data)• Number of days of treatment with opioid analgesics (medians reported, unable to use data)• Survival (not an outcome of this review)• Febrile neutropenia (not an outcome of this review)	
Notes	Sample size calculation: 76 participants required to detect 30% difference in the rate of severe mucositis at 80% power and 5% significance Funding: Amgen (pharmaceutical industry) Declarations/conflicts of interest: not reported Data handling by review authors: data for ITT population used Other information of note: not reported	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “randomly assigned” Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: “randomly assigned” Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “The randomization result was known to the patient as well as to the prac-

Fink 2011 (Continued)

		titioners before the start of therapy”
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: “The randomization result was known to the patient as well as to the practitioners before the start of therapy”
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall attrition was 10% (Group A: 19%; Group B: 0%) for the ITT population. All 7 participants died before therapy started. Although this reason is not related to the outcomes, the balance created by randomisation may have been lost
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Freytes 2004

Methods	Trial design: parallel (3 arms) Location: USA Number of centres: 8 Study duration: not reported Trials registry number: none/unknown
Participants	<p>Inclusion criteria: aged 18 years or older; due to receive autologous HSCT with a conditioning regimen with a high propensity for producing mucositis (typically 50% incidence of NCI-CTC grade 3 or 4 when receiving standard mucositis management) ; Karnofsky performance score of 70%; free of acute or significant chronic dental or periodontal disease at baseline examination</p> <p>Exclusion criteria: previous HSCT; visible oral ulcerations at screening; pregnant or breastfeeding; childbearing potential or not using adequate contraception; history of allergy to <i>Escherichia coli</i>-derived products; posterior subcapsular cataract identified at screening; history of thyroid disease prior to receiving chemotherapy (except for hypothyroidism adequately controlled with replacement therapy); history or clinical evidence of active significant acute or chronic diseases that may affect evaluation or interpretation of the effects of the study medication on mucositis; following medications: interleukin 11, topical steroids, sucralfate, hydrogen peroxide, pilocarpine, misoprostol, oral chlorhexidine rinses, or any agent that would affect the assessment of changes in the appearance of mucositis during the study</p> <p>Cancer type: lymphoma (Group A: 64%; Group B: 71%; Group C: 57%); other haematologic malignancy (Group A: 36%; Group B: 29%; Group C: 43%)</p> <p>Cancer treatment: prior to receiving autologous HSCT, participants received the following conditioning regimens:</p> <ul style="list-style-type: none"> • CBV (cyclophosphamide, etoposide, and carmustine) (Group A: 50%; Group B: 64%; Group C: 43%) • melphalan monotherapy (Group A: 7%; Group B: 21%; Group C: 14%)

	<ul style="list-style-type: none"> • melphalan combination (Group A: 21%; Group B: 14%; Group C: 28%) • cyclophosphamide + TBI (total body irradiation) (Group A: 7%; Group B: 0%; Group C: 14%) • thiotepa + TBI (Group A: 7%; Group B: 0%; Group C: 0%) • cyclophosphamide + busulfan (Group A: 7%; Group B: 0%; Group C: 0%) <p>Age at baseline (years): Group A: mean 54 (SD 10); Group B: mean 47 (SD 10); Group C: mean 51 (SD 15)</p> <p>Gender: Group A: 79% male; Group B: 64% male; Group C: 79% male</p> <p>Number randomised: 42 (Group A: 14; Group B: 14; Group C: 14)</p> <p>Number evaluated: 42 (Group A: 14; Group B: 14; Group C: 14)</p>
Interventions	<p>Comparison: KGF-2 (repifermin) versus placebo</p> <p>Group A: KGF-2 (25 µg/kg) by IV daily for 3 days prior to conditioning regimen and autologous HSCT and then for 10 days after (total dose = 325 µg/kg)</p> <p>Group B: KGF-2 (50 µg/kg) as above (total dose = 650 µg/kg)</p> <p>Group C: placebo as above</p> <p>Compliance: not reported</p> <p>Duration of treatment: 13 treatment days (over a longer period dependent on conditioning regimen)</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: NCI-CTC 0 to 4 scale (incidence of grade 2, 3 or 4, assessed prior to conditioning regimen, on day of HSCT, then 3 times per week until resolution of mucositis) • Oral mucositis: OMAS 0 to 45 scale (reported as mean worst score and mean 3 worst scores, NCI-CTC data used for analysis) • Oral and oropharyngeal pain: 0 (no pain) to 10 (worse pain) scale (assessed on days reported above, reported as mean worst score experienced) • Normalcy of diet: ability to eat 1 to 4 score, where 1 = normal, 2 = only soft solids, 3 = only liquids, 4 = no solids or liquids (assessed on days reported above, reported as mean worst score) • Adverse events (assessed from the start of the intervention until 28 days after the final dose, reported as events with a statistically significant difference between groups or that occurred in at least 50% of participants in any group and differed between groups by at least 10%) • Number of days of treatment with opioid analgesics (assessed as reported for oral mucositis outcome, reported as mean number of days due to mucositis pain, and mean number of days due to all pain; we used the former although acknowledge other studies typically do not specify whether or not they are reporting usage due to mucositis pain) • Pain on swallowing (not an outcome of this review) • Laboratory parameters (not outcomes of this review) • Immunogenicity (not an outcome of this review) • Electrocardiogram abnormalities, chest x-ray assessments and ophthalmologic examinations (not outcomes of this review)
Notes	<p>Sample size calculation: not reported</p> <p>Funding: not reported</p> <p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: we combined the 2 KGF-2 groups to make a single pairwise comparison against placebo and we also made a comparison of the 2 different</p>

KGF-2 dosages against each other Other information of note: not reported		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from correspondence with authors: "The method to implement the random allocation was by central telephone" Comment: centralised randomisation method - likely to be done properly
Allocation concealment (selection bias)	Low risk	Quote from correspondence with authors: "The method to implement the random allocation was by central telephone" Comment: centralised randomisation method - likely to be done properly
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blinded, placebo-controlled" Comment: the use of a placebo and identical schedule of treatment for all 3 arms should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blinded, placebo-controlled" Comment: it is not clear who was blinded. There are subjective elements to the assessment of oral mucositis using the NCI-CTC scale, requiring the patient's assessment of pain/soreness and their ability to swallow but, as the participants were unaware of their group allocation, the assessment of oral mucositis can be considered to be blinded. This would be the same for other subjective outcomes. The objective outcomes are unlikely to be affected by any potential lack of blinding of the outcome assessor(s)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses

Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Gholizadeh 2016

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Iran</p> <p>Number of centres: not reported</p> <p>Study duration: not reported</p> <p>Trials registry number: IRCT2013021812510N1 (mentioned in trial report)</p>
Participants	<p>Inclusion criteria: previously untreated acute lymphoblastic leukaemia patients; aged between 5 and 18 years</p> <p>Exclusion criteria: any other systemic disease; presence of oral mucositis or other oral lesions prior to chemotherapy; history of dermatology or respiratory hypersensitivity; acute lymphoblastic leukaemia recurrence</p> <p>Cancer type: acute lymphoblastic leukaemia (ALL)</p> <p>Cancer treatment: induction chemotherapy protocol consisted of standard risk B-precursor ALL (COG)/dexamethasone, vincristine, L-asparaginase, intrathecal (methotrexate + ara-C + hydrocortisone). The intensification protocol was dexamethasone, vincristine, L-asparaginase/ dexamethasone, cyclophosphamide/6-thioguanine + cytarabine + intrathecal methotrexate</p> <p>Age at baseline (years): Group A: mean 8.8 (SD 2.5); Group B: mean 8.4 (SD 2.2); overall range: 5 to 18</p> <p>Gender: Group A: 49% male; Group B: 49% male</p> <p>Number randomised: 90 (Group A: 45; Group B: 45)</p> <p>Number evaluated: 90 (Group A: 45; Group B: 45)</p>
Interventions	<p>Comparison: KGF (palifermin) versus chlorhexidine</p> <p>Group A: KGF (60 µg/kg) by IV bolus daily for 3 days prior to chemotherapy regimen and then for 3 days after (total dose = 360 µg/kg)</p> <p>Group B: chlorhexidine (concentration not reported) mouthwash used for 1 minute once daily for 3 days prior to chemotherapy regimen and then for 3 days after</p> <p>Compliance: not reported</p> <p>Duration of treatment: 6 treatment days (over an unspecified longer period)</p>
Outcomes	<ul style="list-style-type: none"> Oral mucositis: WHO 0 to 4 scale (measured after 1 and 2 weeks and reported separately for each time point) Adverse events
Notes	<p>Sample size calculation: not reported</p> <p>Funding: not reported</p> <p>Declarations/conflicts of interest: "There is no conflict of interest in relation to this study"</p> <p>Data handling by review authors: we report the data at 2 weeks as they represent the maximum oral mucositis score experienced better than those at 1 week</p>

Other information of note: not reported		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomly assigned to the palifermin or control group by using the table of random numbers" Comment: adequate method used
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly assigned to the palifermin or control group by using the table of random numbers" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comparison with chlorhexidine so blinding not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Each patient was evaluated for oral lesions one and two weeks after the chemotherapy completion by the same specialist who was blind to the type of treatment" and "This limited use of chlorhexidine was to prevent the adverse effects like tooth discoloration and temporally taste changes" Comment: grade 1 on this scale would require the unblinded participant's assessment of soreness but other aspects of the scale are more objective and were assessed by a blinded assessor. Also, blinding may not have been broken by staining/discolouration due to limited use of chlorhexidine
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Australia, Canada, and Europe (Austria, France, Germany, Italy, Spain, UK)</p> <p>Number of centres: 38</p> <p>Study duration: recruitment from January 2005 to August 2007</p> <p>Trials registry number: NCT00131638; 2004-002016-28 (EudraCT number)</p>
Participants	<p>Inclusion criteria: more than 18 years old; resected for pathohistologically documented high-risk stage 2 to 4B SCC of the oral cavity, oropharynx, hypopharynx, or larynx; ECOG score of 0 to 2; at least 2 of 9 areas of the oral or oropharyngeal mucosa due to receive at least 50 Gy RT</p> <p>Exclusion criteria: tumours of the lips, paranasal sinuses, salivary glands, or unknown primary site; metastatic disease; history of chronic pancreatitis or acute pancreatitis within the last year; prior RT to the head and neck region or prior chemotherapy; previous treatment on this study or with other KGFs</p> <p>Cancer type: head and neck: oropharynx (Group A: 47%; Group B: 48%); oral cavity (Group A: 32%; Group B: 27%); larynx (Group A: 11%; Group B: 15%); hypopharynx (Group A: 10%; Group B: 10%); other (Group A: 1%; Group B: 1%)</p> <p>Cancer treatment: after R0 or R1 resection:</p> <ul style="list-style-type: none"> radiotherapy: standard fractionation of once daily 2-Gy fractions, 5 days per week; total 60 Gy (for R0 resection) over 6 weeks, or 66 Gy (for R1 resection) over 7 weeks, both with allowable range of $\pm 15\%$ chemotherapy: cisplatin (100 mg/m²) by IV after appropriate hydration on days 1 and 22 (for R0 resection), or days 1, 22 and 43 (for R1 resection) <p>Age at baseline (years): Group A: mean 56 (SD 8); Group B: mean 57 (SD 9)</p> <p>Gender: Group A: 85% male; Group B: 80% male</p> <p>Number randomised: 186 (Group A: 92; Group B: 94)</p> <p>Number evaluated: 186 (Group A: 92; Group B: 94)</p>
Interventions	<p>Comparison: KGF (palifermin) versus placebo</p> <p>Group A: KGF (120 µg/kg) 3 days prior to start of, and then once per week during radiochemotherapy, i.e. 7 doses for those with R0 resection, 8 doses for those with R1 resection (total dose = 840 µg/kg or 960 µg/kg respectively)</p> <p>Group B: same schedule with placebo</p> <p>Mode of administration not described but presumably IV as in other KGF studies</p> <p>Compliance: 78% of participants in KGF group completed all planned doses compared to 86% in placebo group</p> <p>Duration of treatment: 7 or 8 treatment days (over 7 or 8 weeks), depending on R0 or R1 resection respectively</p>
Outcomes	<ul style="list-style-type: none"> Oral mucositis: WHO 0 to 4 scale (assessed twice weekly by trained evaluators during radiochemotherapy and then until either mucositis had reduced to grade 2 or lower or week 15, whichever occurred first, maximum score reported) (duration and time to onset of grade 3 to 4 oral mucositis also measured but not outcomes of this review) Interruptions to cancer treatment: incidence of 5 or more missed consecutive RT fractions; incidence of chemotherapy delays/discontinuations Oral pain: OMWQ-HN 0 (no soreness) to 4 (extreme soreness) scale for mouth and throat soreness

	<ul style="list-style-type: none">• Normalcy of diet (measured as incidence of supplemental feeding by TPN, PEG, nasogastric tube, or IV hydration) (broken down by overall supplemental feeding and also where due to oral mucositis; we used the latter although acknowledge other studies do not specify reason for supplemental feeding)• Adverse events: reported as those with a difference in incidence of at least 5% between arms• Use of opioid analgesics (total dose reported but not an outcome of this review)• Xerostomia (not an outcome of this review)• Weight change (not an outcome of this review)• Laboratory assessments (not an outcome of this review)• Survival (not an outcome of this review)	
Notes	<p>Sample size calculation: assuming 60% of placebo group would develop grade 3 to 4 mucositis, 90 per group required to detect a reduction of at least 25% at 90% power and 5% significance</p> <p>Funding: “This study was supported by Amgen” (Amgen also named as sponsor on trials registry - pharmaceutical industry)</p> <p>Declarations/conflicts of interest: some authors had both employment or leadership positions and stock ownership within Amgen</p> <p>Data handling by review authors: N/A</p> <p>Other information of note: study originally randomised participants to 3 arms (180 µg/kg once per week for 7 weeks, 180 µg/kg once per week for 4 weeks followed by placebo for the next 3 doses, or placebo throughout) but, after 1 serious adverse event of respiratory insufficiency reported in 1 of the first 10 participants, the data monitoring committee decided to restart the study using 120 µg/kg doses, excluding the 17 randomised participants from the efficacy assessments. The arm with KGF for 4 weeks followed by placebo was stopped due to slow recruitment, after enrolment of 38 participants, and the results analysed in a separate appendix</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: “Random assignment was made by a centralized interactive voice response system”</p> <p>Comment: large multicentre trial using high-tech randomisation method - likely to be done properly</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: “Random assignment was made by a centralized interactive voice response system”</p> <p>Comment: large multicentre trial using high-tech randomisation method - likely to be done properly</p>

Henke 2011 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double-blind, randomized, placebo-controlled” Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double-blind, randomized, placebo-controlled” Comment: it is not clear who was blinded. There are subjective elements to the assessment of lower grades of oral mucositis using the WHO scale, requiring the patient’s assessment of pain/soreness and their ability to swallow. Higher grades have more objective elements so may not be affected by potential lack of blinding of the assessor. This would be the same for other subjective and objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Hosseinjani 2017

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Tehran University of Medical Sciences, Tehran, Iran</p> <p>Number of centres: 1</p> <p>Study duration: February 2014 to March 2015</p> <p>Trials registry number: IRCT2015042518842N8 (mentioned in trial report)</p>
Participants	<p>Inclusion criteria: aged 18 years or older with non-Hodgkin’s lymphoma, Hodgkin’s disease or multiple myeloma; due to receive autologous HSCT; adequate cardiac, pulmonary, renal and hepatic function</p> <p>Exclusion criteria: Karnofsky performance score less than 70%; participation in another study using an unlicensed product</p> <p>Cancer type: haematologic: non-Hodgkin’s lymphoma (Group A: 25%; Group B: 25%); Hodgkin’s disease (Group A: 23%; Group B: 23%); multiple myeloma (Group A: 53%; Group B: 53%)</p> <p>Cancer treatment: prior to receiving autologous HSCT, participants received the following conditioning regimens:</p> <ul style="list-style-type: none"> • Hodgkin’s/non-Hodgkin’s: high-dose combination chemotherapy (carboplatin 750 mg/m² IV daily for 2 days, etoposide 300 mg/m² IV daily for 2 days, cytarabine 300mg/m²/dose IV 2 doses in each day for 2 days, and melphalan 140 mg/m² IV for 1

	<div>day)</div> <ul style="list-style-type: none">Multiple myeloma: high-dose melphalan (100 mg/m² IV daily for 2 days) <p>Age at baseline (years): Group A: mean 43 (SD 14); Group B: mean 45 (SD 16)</p> <p>Gender: Group A: 55% male; Group B: 48% male</p> <p>Number randomised: 80 (Group A: 40; Group B: 40)</p> <p>Number evaluated: 80 (Group A: 40; Group B: 40)</p>	
Interventions	<p>Comparison: Erythropoietin (recombinant human) versus placebo</p> <p>Group A: 50 IU/mL erythropoietin mouthwash in aqueous vehicle (sodium benzoate, sodium citrate, citric acid, sodium hydroxide, sugar and distilled water) supplied in glass bottle stored at 4°C, 15 mL 4 times daily, starting from the first day of conditioning chemotherapy until 14 days after HSCT or until discharge from hospital (i.e. neutrophil recovery), whichever occurred first, oral intake not permitted for 1 hour following mouth-washing</p> <p>Group B: same schedule with placebo (aqueous vehicle-only)</p> <p>All participants received oral hygiene care in addition to 20 drops of nystatin every 3 hours, mouthwashes containing 10 mL chlorhexidine 0.02% plus 10 mL diluted povidone iodine every 3 hours</p> <p>Compliance: “However, it was a limitation of our study that EPO mouthwash administration might be affected by patients’ low compliance” (no data reported)</p> <p>Duration of treatment: variable and dependent on neutrophil recovery</p>	
Outcomes	<ul style="list-style-type: none">Oral mucositis: WHO 0 to 4 scale (assessed daily by single trained pharmacist starting from the first day of conditioning chemotherapy and then until either 21 days after HSCT or mucositis had resolved, whichever occurred first, maximum score reported) (duration and time to onset reported but not outcomes of this review)Number of days in hospitalUse of opioid analgesics (incidence reported but not an outcome of this review)Blood measurements (not an outcome of this review)Incidence and duration of fever (not an outcome of this review)	
Notes	<p>Sample size calculation: 40 per group required assuming a 30% decrease in incidence of grade 2 to 4 mucositis at 5% significance and 80% power</p> <p>Funding: “There was no applicable funding source for the clinical trial”</p> <p>Declarations/conflicts of interest: “The authors have no conflict of interests to report”</p> <p>Data handling by review authors: there is a discrepancy in the incidence of grade 2 to 4 mucositis between Figure 2 and Table 2 (the latter has 1 extra event per group). However, this does not change the effect estimate. We have used the data in Table 2 as it reports numbers of participants along with percentages</p> <p>Other information of note: not reported</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients were randomly allocated. ..in a blocked randomization schedule” and “Both patient randomization and drug

		<p>preparation were performed in the pharmaceutical laboratory of Pharmacy Department”</p> <p>Comment: method of random sequence generation not described but done by university hospital pharmacy and therefore probably done adequately</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: “Both patient randomization and drug preparation were performed in the pharmaceutical laboratory of Pharmacy Department”</p> <p>Comment: not explicitly described but pharmacy-controlled randomisation should have ensured concealment of the random sequence from those recruiting participants</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: “double-blind, randomized, placebo-controlled” and “The study participants, the attending physician and the outcome assessor were all blind to the treatment assignment” and “There were no differences in colour, flavour, taste or container of the study drug and the placebo”</p> <p>Comment: the use of a placebo should have ensured that blinding was successful</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: “double-blind, randomized, placebo-controlled” and “The study participants, the attending physician and the outcome assessor were all blind to the treatment assignment”</p> <p>Comment: all parties were blinded</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: USA (16 sites) and Australia (4 sites)</p> <p>Number of centres: 20</p> <p>Study duration: December 2005 to November 2008</p> <p>Trials registry number: NCT00189488 (mentions obsolete number in trial report: NCT00964899)</p>
Participants	<p>Inclusion criteria: aged 18 years or older with haematologic malignancy (including myelodysplastic syndromes) and due to receive allogeneic SCT (marrow or PBPC) after a conditioning regimen; Karnofsky performance score of 70% or more; related donor or HLA-matched unrelated donor identical at 6/6 HLA-A, -B and -DRB1 loci (molecular typing of class I and class II for unrelated donors)</p> <p>Exclusion criteria: other malignancies; prior SCT; previous use of KGF; active infection or oral mucositis; congestive heart failure (NYHA class III or IV); use of a T-cell depleted graft for GVHD prophylaxis; inadequate renal, liver or pulmonary function; pregnant or breastfeeding; refusal to use adequate contraception during study; participation in another investigational device or drug trial in previous 30 days</p> <p>Cancer type: haematologic: leukaemia (Group A: 71%; Group B: 79%); myelodysplastic syndrome (Group A: 16%; Group B: 12%); non-Hodgkin's lymphoma (Group A: 12%; Group B: 8%); multiple myeloma (Group A: 0%; Group B: 1%); Hodgkin's disease (Group A: 1%; Group B: 0%)</p> <p>Cancer treatment: prior to receiving allogeneic SCT on day 0, participants received 1 of the following conditioning regimens from day -11 to -2:</p> <ul style="list-style-type: none"> • cyclophosphamide plus TBI with or without etoposide • TBI plus etoposide • melphalan plus TBI > 11 Gy • busulfan plus cyclophosphamide • busulfan plus melphalan (fully ablative doses) • fludarabine plus melphalan (fully ablative doses) <p>Participants received methotrexate (with a calcineurin inhibitor - either cyclosporine or tacrolimus) for GVHD prophylaxis on days 1, 3 and 6 (planned), and on day 11 (if toxicity allowed) at doses of 15 mg/m², 10 mg/m², 10 mg/m² and 10 mg/m² respectively</p> <p>Age at baseline (years): Group A: median 42 (range 18 to 62); Group B: median 44 (range 18 to 64)</p> <p>Gender: Group A: 52% male; Group B: 63% male</p> <p>Number randomised: 155 (Group A: 77; Group B: 78)</p> <p>Number evaluated: 155 (Group A: 77; Group B: 78)</p>
Interventions	<p>Comparison: KGF (palifermin) versus placebo</p> <p>Group A: KGF (60 µg/kg) by IV bolus daily for 3 days prior to start of conditioning therapy, then a single 180 µg/kg dose after conditioning, but often 1 or 2 days before SCT (total dose = 360 µg/kg)</p> <p>Group B: same schedule with placebo</p> <p>Compliance: received at least 1 dose: Group A: 99%; Group B: 96%; received all doses: Group A: 92%; Group B: 88%</p> <p>Duration of treatment: 4 treatment days (over roughly 14 days)</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale (reported as incidence of grade 2 to 4 i.e. moderate to severe, and grade 3 to 4 i.e. severe, assessed daily by trained evaluators)

	from day -11 (first day of conditioning) and then until hospital discharge or day 28, whichever occurred first) (duration also measured but not an outcome of this review) <ul style="list-style-type: none">• Normalcy of diet (measured as incidence of TPN)• Adverse events• Use of opioid analgesics (incidence reported but not an outcome of this review)• Incidence and severity of acute GVHD (not an outcome of this review)	
Notes	Sample size calculation: based on GVHD (not met due to early stopping) Funding: “This study was supported by research funding from Amgen Inc. Jonathan Latham of PharmaScribe, LLC received funding from Amgen Inc. to provide assistance with the preparation of the manuscript. Xuesong Guan of Amgen Inc. provided assistance with statistical analyses” (pharmaceutical industry) Declarations/conflicts of interest: some authors were employees and stockholders of Amgen and some received compensation from Amgen for consultation Data handling by review authors: N/A Other information of note: planned sample size was 200 participants but the study was stopped due to slow recruitment	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Subjects were randomly assigned. ..” Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: “Subjects were randomly assigned. ..” Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double-blind, placebo-controlled” Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double-blind, placebo-controlled” Comment: it is not clear who was blinded but grades 2 to 4 on the WHO scale are sufficiently objective and unlikely to be affected by any lack of blinding of the assessors

Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Katano 1995

Methods	Trial design: parallel (2 arms) Location: Saga Medical School, Saga, Japan Number of centres: 1 Study duration: not reported Trials registry number: none/unknown
Participants	Inclusion criteria: breast cancer patients Exclusion criteria: not reported Cancer type: breast: primary advanced (Group A: 2; Group B: 5); inflammatory (Group A: 4; Group B: 1); recurrent (Group A: 1; Group B: 1) Cancer treatment: preoperative IA high-dose adriamycin (10 mg to 40 mg every 2 to 3 days to a total dose of 70 mg to 170 mg) Age at baseline (years): Group A: mean 53 (SD 11; range 38 to 69); Group B: mean 52 (SD 10; range 45 to 69) Gender: all female Number randomised: 14 (Group A: 7; Group B: 7) Number evaluated: 14 (Group A: 7; Group B: 7)
Interventions	Comparison: G-CSF versus no treatment Group A: G-CSF (125 µg) by daily subcutaneous injection until leukocyte counts > 8000/mm ³ ; timing in relation to chemotherapy not specifically reported, but the group was further divided into 2 subgroups where one (n = 4) received G-CSF during/as an adjunct to the chemotherapy, and the other (n = 3) received G-CSF afterwards (after the leukocyte counts were likely to drop below 2000/mm ³) Group B: no treatment Compliance: not reported Duration of treatment: variable and dependent on leukocyte recovery (to > 8000/mm ³)
Outcomes	<ul style="list-style-type: none"> Oral mucositis: WHO 0 to 4 scale (assessed once 1 to 7 days prior to chemotherapy and then every day afterwards by a single experienced examiner, reported as incidence of grade 2 to 4) (duration of grade 2 to 4 also measured but not an outcome of this review) Blood measurements (not an outcome of this review) Alopecia (not an outcome of this review) Adult respiratory distress syndrome (not an outcome of this review) Fever (not an outcome of this review)

Notes	Sample size calculation: not reported Funding: “G-CSF (Neutrogin) was provided by Chugai Pharmaceutical” Declarations/conflicts of interest: not reported Data handling by review authors: the data for incidence of mucositis were presented in subgroups of those receiving G-CSF during or after chemotherapy but we used the overall data in our meta-analyses Other information of note: both cases of mucositis were in the subgroup who received G-CSF after chemotherapy. Oral mucositis may have already begun to develop in this subgroup	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “randomized into two groups” Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: “randomized into two groups” Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comparison with no treatment so blinding not possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It would be possible to blind the outcome assessor, as the data we used were assessed by an examiner looking for erythema and ulcers. However, it was not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Seoul National University Hospital, Seoul, South Korea</p> <p>Number of centres: 1</p> <p>Study duration: recruitment from March 2009 to August 2014</p> <p>Trials registry number: NCT00845819 (mentioned in trial report)</p>
Participants	<p>Inclusion criteria: aged 18 years or older with haematologic malignancy; due to receive intensive chemotherapy followed by autologous or allogeneic HSCT; normal oral cavity (grade 0 mucositis); ECOG score of 0 to 2</p> <p>Exclusion criteria: received chemotherapy, radiotherapy or surgery within previous 3 weeks; history of allergy to the intervention or similar drugs; participation in other clinical trials within the previous 4 weeks with the potential to affect study results</p> <p>Cancer type: haematologic: multiple myeloma (Group A: 57%; Group B: 55%); lymphoma (Group A: 36%; Group B: 38%); other (Group A: 7%; Group B: 7%)</p> <p>Cancer treatment: prior to receiving autologous (Group A: 96%; Group B: 96%) or allogeneic HSCT, participants received the following conditioning regimens:</p> <ul style="list-style-type: none"> • high-dose melphalan (Group A: 57%; Group B: 57%) • mitoxantrone-etoposide-cytarabine-melphalan (Group A: 15%; Group B: 23%) • busulfan-etoposide-cytarabine-melphalan (Group A: 19%; Group B: 16%) • other (Group A: 9%; Group B: 4%) <p>Age at baseline (years): Group A: median 53 (range 18 to 65); Group B: median 51 (range 19 to 65)</p> <p>Gender: Group A: 49% male; Group B: 54% male</p> <p>Number randomised: 138 (Group A: 69; Group B: 69)</p> <p>Number evaluated: 136 (Group A: 67; Group B: 69)</p>
Interventions	<p>Comparison: EGF (recombinant human) versus placebo</p> <p>Group A: EGF (50 µg/mL) daily by oral spray, applied twice daily, sprayed (6 sprays per application) over the entire oral mucosa and then swallowed, no oral intake for 30 minutes afterwards; starting on first day of conditioning therapy and continuing until absolute neutrophil count recovered more than 1000 µL for 3 days and mucositis had resolved</p> <p>Group B: placebo as above</p> <p>Compliance: median patient compliance rate: Group A: 93% (range 35% to 100%); Group B: 92% (range 18% to 100%)</p> <p>Duration of treatment: variable and dependent on neutrophil recovery/resolution of mucositis</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: NCI-CTC (version 3.0) 0 to 4 scale (assessed daily during study period by researchers, reported as incidence of grade 2 to 4 i.e. moderate to severe, and grade 3 to 4 i.e. severe) (duration and time to onset reported but not outcomes of this review) • Oral pain: mouth and throat soreness 0 to 10 scale (reported as AUC median/range and only for those who had grade 2 to 4 mucositis - data not usable) • Quality of life: modified OMDQ (reported as AUC median/range and only for those who had grade 2 to 4 mucositis - data not usable) • Normalcy of diet (use of total parenteral nutrition) • Adverse events (NCI CTC version 3.0) • Number of days in hospital (listed as an outcome but not reported anywhere in the results - data not usable)

	<ul style="list-style-type: none">• Number of days of treatment with opioid analgesics (reported as median/range and only for those who had grade 2 to 4 mucositis - data not usable)• Incidence of febrile neutropenia (not an outcome of this review)• Blood infections (not an outcome of this review)• Antibiotic use (not an outcome of this review)• Clinical laboratory measurements (not outcomes of this review)	
Notes	<p>Sample size calculation: 62 participants per group required to detect 27% difference in incidence of grade 2 to 4 mucositis with 80% power and 5% significance</p> <p>Funding: multiple government grants; Daewoong Pharmaceutical Company (Seoul, Korea) only supplied interventions but provided no further funding and had no involvement with data collection, analysis or manuscript writing</p> <p>Declarations/conflicts of interest: none apparent</p> <p>Data handling by review authors: N/A</p> <p>Other information of note: not reported</p>	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned. ..using a computer-generated randomization protocol, by the Medical Research Collaborating Center, Seoul National University Hospital" Comment: adequate method used
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly assigned. ..using a computer-generated randomization protocol, by the Medical Research Collaborating Center, Seoul National University Hospital" Comment: although concealment not explicitly mentioned, use of centralised/third party randomisation - likely to be done properly
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo-controlled, double-blind" and "clinicians, patients, and investigators responsible for assessing outcomes and analyzing data were masked to treatment assignments" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "placebo-controlled, double-blind" and "clinicians, patients, and investigators responsible for assessing outcomes and analyzing data were masked to treatment as-

		signments” Comment: all parties were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 of 138 randomised participants were not included in the analysis
Selective reporting (reporting bias)	Low risk	Although most of the data were not usable in this review, this does not seem to be due to selective reporting
Other bias	Low risk	No other sources of bias are apparent

Le 2011

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Canada, USA and Europe (Hungary, Poland, Austria, Germany, Italy, Czech Republic)</p> <p>Number of centres: 46</p> <p>Study duration: recruitment started August 2005, 4-month follow-up finished September 2007</p> <p>Trials registry number: NCT00101582; 2005-000213-35 (EudraCT number)</p>
Participants	<p>Inclusion criteria: newly diagnosed, unresected stage 3 to 4B SCC of the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx; no evidence of secondary malignancy; at least 2 of 9 areas of the oral or oropharyngeal mucosa due to receive more than 50 Gy RT</p> <p>Exclusion criteria: not reported</p> <p>Cancer type: head and neck: oropharynx (Group A: 59%; Group B: 54%); oral cavity (Group A: 5%; Group B: 10%); larynx (Group A: 17%; Group B: 10%); hypopharynx (Group A: 15%; Group B: 23%); nasopharynx (Group A: 4%; Group B: 3%)</p> <p>Cancer treatment:</p> <ul style="list-style-type: none"> • Radiotherapy: standard fractionation of once daily 2-Gy fractions, 5 days per week; total 70 Gy over 7 weeks • Chemotherapy: cisplatin (100 mg/m²) by IV infusion on days 1, 22 and 43 <p>Age at baseline (years): Group A: mean 56 (SD 9); Group B: mean 55 (SD 8)</p> <p>Gender: Group A: 84% male; Group B: 85% male</p> <p>Number randomised: 188 (Group A: 94; Group B: 94)</p> <p>Number evaluated: 188 (Group A: 94; Group B: 94)</p>
Interventions	<p>Comparison: KGF (palifermin) versus placebo</p> <p>Group A: KGF (180 µg/kg) by IV bolus over 30 to 60 seconds, 3 days prior to start of, and then once per week during radiochemotherapy, i.e. 8 doses (total dose = 1440 µg/kg)</p> <p>Group B: same schedule with placebo</p> <p>Compliance: 93% (SD 19%) of planned KGF doses were administered compared to 96% (SD 14%) in placebo group</p> <p>Duration of treatment: 8 treatment days (over 8 weeks)</p>

Outcomes	<ul style="list-style-type: none">• Oral mucositis: WHO 0 to 4 scale (assessed twice weekly by trained evaluators during radiochemotherapy and then until either mucositis had reduced to grade 2 or lower or week 15, whichever occurred first, maximum score reported) (duration and time to onset of grade 3 to 4 oral mucositis also measured but not outcomes of this review)• Interruptions to cancer treatment: incidence of 5 or more missed consecutive RT fractions; incidence of chemotherapy delays/discontinuations• Oral pain: OMWQ-HN 0 (no soreness) to 4 (extreme soreness) scale for mouth and throat soreness (assessed twice weekly by trained evaluators during radiochemotherapy)• Normalcy of diet (measured as incidence of supplemental feeding by TPN, PEG, nasogastric tube, or IV hydration) (duration of supplemental feeding also reported but not used for analysis)• Adverse events: NCI-CTC (version 3.0) reported separately for those related to study drugs• Use of opioid analgesics (total dose reported but not an outcome of this review)• Xerostomia (not an outcome of this review)• Survival (not an outcome of this review)• Laboratory assessments (not an outcome of this review)• Antipalifermin antibodies (not an outcome of this review)	
Notes	<p>Sample size calculation: assuming 60% of placebo group would develop grade 3 to 4 mucositis, 90 per group required to detect a reduction of at least 25% at 90% power and 5% significance</p> <p>Funding: “Supported by Amgen” (Swedish Orphan Biovitrum named as sponsor on trials registry, Amgen named as collaborator - both pharmaceutical industry)</p> <p>Declarations/conflicts of interest: some authors had both employment or leadership positions and stock ownership within Amgen; some authors had received research funding from Amgen</p> <p>Data handling by review authors: N/A</p> <p>Other information of note: not reported</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “A centralized randomization system assigned patients to either palifermin or placebo in a 1:1 ratio” Comment: large multicentre trial using centralised randomisation method - likely to be done properly
Allocation concealment (selection bias)	Low risk	Quote: “A centralized randomization system assigned patients to either palifermin or placebo in a 1:1 ratio” Comment: large multicentre trial using centralised randomisation method - likely

Le 2011 (Continued)

		to be done properly
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “placebo-controlled, double-blind” Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “placebo-controlled, double-blind” Comment: it is not clear who was blinded. There are subjective elements to the assessment of lower grades of oral mucositis using the WHO scale, requiring the patient’s assessment of pain/soreness and their ability to swallow. Higher grades have more objective elements so may not be affected by potential lack of blinding of the assessor. This would be the same for other subjective and objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Linch 1993

Methods	Trial design: parallel (5 arms) Location: UK Number of centres: 12 Study duration: recruitment from August 1989 to July 1990 Trials registry number: none/unknown
Participants	Inclusion criteria: adults due to receive BMT after conditioning Exclusion criteria: myeloid malignancies Cancer type: mixed haematologic and solid (not reported by group): Hodgkin’s disease (29%); non-Hodgkin’s lymphoma (33%); multiple myeloma (Group A: 20%); ALL (15%); solid (3%) Cancer treatment: prior to receiving BMT (autologous 84%; allogeneic 16%), participants received a conditioning regimen which consisted of chemotherapy only (71%) or with TBI (29%) Age at baseline (years): median 36 (range 17 to 64) (not reported by group) Gender: 69% male (not reported by group) Number randomised: 121 (Group A: 96; Group B: 25); Group A represents 4 arms with different dosages Number evaluated: 121 (Group A: 96; Group B: 25)

Interventions	Comparison: G-CSF versus placebo Group A: G-CSF (2 µg/kg, 5 µg/kg, 10 µg/kg or 15 µg/kg) by 30-minute IV daily starting from the day after BMT transplant and continuing until neutrophil count was > 1.0 x 10 ⁹ /L for 3 consecutive days or until day 28, whichever occurred first Group B: as above but with placebo Compliance: not reported Duration of treatment: variable and dependent on neutrophil recovery	
Outcomes	<ul style="list-style-type: none">• Oral mucositis: unspecified scale (frequency of measurement not mentioned, no usable data)• Adverse events• Number of days in hospital (median reported, no usable data)• Neutropenia-related outcomes (not outcomes of this review)• Antibiotic use (not an outcome of this review)• Fever (not an outcome of this review)• Sepsis (not an outcome of this review)• Blood product use (not an outcome of this review)	
Notes	Sample size calculation: not reported Funding: “Financial support for this trial was provided by Chugai Rhone Poulenc” (pharmaceutical industry) Declarations/conflicts of interest: 1 author was employed by the funders Data handling by review authors: oral mucositis reported narratively in additional table Other information of note: G-CSF administration only began after the conditioning and BMT transplant were completed, by which point oral mucositis may have already begun to develop (although time scale of conditioning/BMT transplant not reported)	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients were randomised...in blocks of five by a computer-generated randomisation schedule” Comment: adequate method used
Allocation concealment (selection bias)	Unclear risk	Quote: “Patients were randomised...in blocks of five by a computer-generated randomisation schedule” Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “single blind...vehicle-controlled” Comment: the use of a placebo (the ‘vehicle’) should have ensured that blinding was successful

Linch 1993 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: “single blind...vehicle-controlled” Comment: the quote implies that outcome assessment was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	High risk	Oral mucositis not mentioned in the methods section as 1 of the study end points. It is only mentioned in the results narratively as there being no difference between any group, but with no data or P value
Other bias	Low risk	No other sources of bias are apparent

Lucchese 2016a

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Vita-Salute San Raffaele University Hospital, Milan, Italy</p> <p>Number of centres: 1</p> <p>Study duration: conducted from April 2009 to January 2015</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: children aged 7 years or older with B-cell lineage acute lymphoblastic leukaemia; scheduled to receive autologous HSCT after a conditioning regimen; Karnofsky performance score of 70 or more; were to have at least 1.5×10^6 CD34+ cells reinfused per kilogram available for transplant; adequate cardiac, pulmonary, renal and hepatic function</p> <p>Exclusion criteria: not reported</p> <p>Cancer type: B-cell lineage acute lymphoblastic leukaemia</p> <p>Cancer treatment: prior to receiving autologous HSCT (on day 0), participants received a conditioning regimen which consisted of TBI delivered in 8 fractions over 3 days (-3 to -1) with at least 6 hours between fractions, followed by chemotherapy on day -1 (type and dose of radiotherapy and chemotherapy not reported)</p> <p>Age at baseline (years): Group A: median 11 (range 7 to 16); Group B: median 11 (range 7 to 16)</p> <p>Gender: Group A: 52% male; Group B: 44% male</p> <p>Number randomised: 60 (Group A: 30; Group B: 30)</p> <p>Number evaluated: 54 (Group A: 27; Group B: 27)</p>
Interventions	<p>Comparison: KGF (palifermin) versus placebo</p> <p>Group A: KGF (60 µg/kg) by IV, on days -6 (3 days prior to start of conditioning regimen), -5 and -4, and on days 0 (the day of HSCT), 1, and 2 after transplant (total dose = 360 µg/kg)</p> <p>Group B: same schedule with placebo</p> <p>Compliance: not reported</p> <p>Duration of treatment: 6 treatment days (over 9 days)</p>

Outcomes	<ul style="list-style-type: none">• Oral mucositis: WHO 0 to 4 scale (assessed daily by same clinician from day -7 to day 28, or until severe mucositis had reduced to grade 0, 1, or 2, data in text and figure 2 do not agree with data in table 3) (duration of grade 2 to 4 and 3 to 4 oral mucositis also measured but not an outcome of this review)• Oral pain: OMDQ 5-point scale for mouth and throat soreness (higher = worse pain) (assessed daily by participant, reported as AUC, not used)• Normalcy of diet (methods states incidence of supplemental feeding by TPN but only duration is reported, yet text states enteral and table states parenteral, not used for analysis) (patient-reported difficulty eating and drinking also assessed daily, both using OMDQ 0 (no difficulty) to 5 (unable to do) scale, but the means are reported as whole numbers, data not used)• Adverse events: NCI-CTC (version 4.0)• Opioid analgesic use (reported as quantity per day; number of days of treatment with opioid analgesics is an outcome of this review but only medians were reported, and therefore we did not use these data)• GVHD incidence and severity (not an outcome of this review)• Fever with neutropenia (not an outcome of this review)• HSV incidence (not an outcome of this review)• Candidiasis incidence (not an outcome of this review)• Superinfections incidence (not an outcome of this review)• Blood measurements (not an outcome of this review)	
Notes	<p>Sample size calculation: numbers required not reported but was estimated at 80% power and 5% significance</p> <p>Funding: “This work was performed with Departmental funding only”</p> <p>Declarations/conflicts of interest: the authors report that they have no conflict of interest (supplemental material on journal website)</p> <p>Data handling by review authors: we emailed the lead author June 2017 for clarification of the oral mucositis data but, until we receive a response, we are unable to use those data</p> <p>Other information of note: unclear definitions of ulcerative (should be grade 2 to 4) and severe (should be grade 3 to 4): “...ulcerative OM (WHO grades 3 and 4), incidence and duration of severe OM (WHO grades 3 and 4)...”</p>	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: “A centralized randomization system assigned patients either to palifermin or conventional treatment in a 1:1 ratio..... .The statistician gave randomization list to the pharmacy, so the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment”</p> <p>Comment: randomisation ‘system’ used and done by a statistician, likely to be done</p>

		properly
Allocation concealment (selection bias)	Low risk	<p>Quote: “A centralized randomization system assigned patients either to palifermin or conventional treatment in a 1:1 ratio..... The statistician gave randomization list to the pharmacy, so the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment”</p> <p>Comment: centralised randomisation with pharmacy assigning participants to groups</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: “double-blind, placebo-controlled” and “The statistician gave randomization list to the pharmacy, so the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment. The pharmacy provided the research team with the blinded study medication”</p> <p>Comment: the use of a placebo should have ensured that blinding was successful</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: “The statistician gave randomization list to the pharmacy, so the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment. The pharmacy provided the research team with the blinded study medication”</p> <p>Comment: outcome assessors were clearly blinded</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition was same in both groups (10%) with the same reason given
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Vita-Salute San Raffaele University Hospital, Milan, Italy</p> <p>Number of centres: 1</p> <p>Study duration: conducted from April 2010 to January 2014</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: children aged 9 to 15 years with B-cell lineage acute lymphoblastic leukaemia; scheduled to receive allogeneic HSCT after a conditioning regimen</p> <p>Exclusion criteria: not reported</p> <p>Cancer type: B-cell lineage acute lymphoblastic leukaemia</p> <p>Cancer treatment: prior to receiving allogeneic HSCT, participants received a conditioning regimen of a total of 12 Gy TBI delivered in 8 fractions of 1.5 Gy twice daily over 4 days</p> <p>Age at baseline (years): Group A: median 12 (range 8 to 15); Group B: median 12 (range 8 to 15)</p> <p>Gender: Group A: 50% male; Group B: 55% male</p> <p>Number randomised: 46 (Group A: 24; Group B: 22)</p> <p>Number evaluated: 46 (Group A: 24; Group B: 22)</p>
Interventions	<p>Comparison: KGF (palifermin) versus placebo</p> <p>Group A: KGF (60 µg/kg) by IV, for 3 days prior to start of conditioning regimen and for 3 days after completion (total dose = 360 µg/kg)</p> <p>Group B: same schedule with placebo</p> <p>Compliance: not reported</p> <p>Duration of treatment: 6 treatment days (over unclear period of time - not fully described)</p>
Outcomes	<ul style="list-style-type: none"> Oral mucositis: WHO 0 to 4 scale (assessed by the clinical research team at baseline, days 1, 2, 3 (it is not clear when this is in relation to the cancer treatment or study treatment) and at the end of the cycle - "All of these results were confirmed at the last follow-up (60 days)" - it is not clear how they have been confirmed if, for example, OM has resolved by 60 days; it is not clear whether or not there were multiple cycles, incidence of each grade does not add up or make sense or match the data in table 3) (duration of grade 2 to 4 and 3 to 4 oral mucositis also measured but not an outcome of this review) Normalcy of diet (duration of supplemental feeding by TPN, not used for analysis) (patient-reported difficulty eating and drinking assessed using OMDQ 0 (no difficulty) to 5 (unable to do) scale, but the means are reported as whole numbers, data not used) Adverse events Opioid analgesic use (number of days of treatment with opioid analgesics (morphine) reported but unclear if mean/median and no SD or P value reported; unable to use data; also reported as quantity per day but not an outcome of this review)
Notes	<p>Sample size calculation: not reported</p> <p>Funding: "This work has been performed with departmental funding only"</p> <p>Declarations/conflicts of interest: "The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript"</p> <p>Data handling by review authors: we emailed the lead author June 2017 for clarification of the oral mucositis data but, until we receive a response, we are unable to use those</p>

	data	
	Other information of note: “Patients who had severe (grade 3 or 4) OM during blinded cycles received open-label palifermin at the same dosages as in the other group. The research team assessed patients for OM at baseline before the cycle; at days 1, 2, 3 and at the end of the transplant cycle.” - nowhere else in the report suggests that there were multiple cycles of treatment; unclear definitions of ulcerative mucositis i.e. described correctly in one section as grades 2 to 4, but described in another section as grades 1 to 4	
Risk of bias		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “No stratification was performed and two distinct computer-generated a randomization lists. The statistician gave both randomization lists to the pharmacy, so the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment” Comment: adequate method done by a statistician (although it is unclear why there were 2 lists)
Allocation concealment (selection bias)	Low risk	Quote: “No stratification was performed and two distinct computer-generated a randomization lists. The statistician gave both randomization lists to the pharmacy, so the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment” Comment: randomisation ‘system’ used and done by a statistician, likely to be done properly
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double-blind, placebo-controlled” and “The statistician gave both randomization lists to the pharmacy, so the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment. The pharmacy provided the research team with the blinded study medication” Comment: the use of a placebo should have ensured that blinding was successful

Lucchese 2016b (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The statistician gave both randomization lists to the pharmacy, so the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment. The pharmacy provided the research team with the blinded study medication" Comment: outcome assessors were clearly blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Makkonen 2000

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Turku University Central Hospital and Helsinki University Central Hospital, Finland</p> <p>Number of centres: 2</p> <p>Study duration: recruitment from November 1994 to August 1996</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: scheduled to receive total target dose of at least 56 Gy to the oropharyngeal mucosa</p> <p>Exclusion criteria: prior chemotherapy or radiotherapy; concurrent use of anticholinergic drugs; autoimmune thrombocytopenic purpura; WHO performance status higher than 2</p> <p>Cancer type: head and neck: mobile tongue (Group A: 30%; Group B: 20%); oral cavity, other (Group A: 40%; Group B: 25%); oropharynx (Group A: 20%; Group B: 15%); nasopharynx (Group A: 5%; Group B: 10%); supraglottic larynx (Group A: 5%; Group B: 15%); hypopharynx (Group A: 0%; Group B: 15%)</p> <p>Cancer treatment:</p> <ul style="list-style-type: none"> conventional radiotherapy (Group A: 50%; Group B: 50%): 1.9 Gy to 2 Gy daily fractions, 5 fractions per week hyperfractionated radiotherapy (Group A: 50%; Group B: 50%): 1.6 Gy fractions twice per day with minimum 6 hours between fractions, to a total dose of 38.4 Gy; planned break of 9 to 12 days during which the mucosa healed in order to allow further doses to a total of 56 Gy to 73 Gy; overall treatment time was 5 to 6 weeks <p>Total target dose: Group A: median 65 Gy (range 56 to 68); Group B: median 66 Gy (range 58 to 73); oral surgery prior to RT: Group A: 20%; Group B: 30%; oral surgery after radiotherapy: 23 (not reported by group)</p> <p>Age at baseline (years): Group A: mean 63 (SD 10; range 47 to 87); Group B: mean 59 (SD 13; range 33 to 79)</p>

	Gender: Group A: 60% male; Group B: 55% male Number randomised: 40 (Group A: 20; Group B: 20) Number evaluated: unclear; results presented as percentages	
Interventions	Comparison: GM-CSF (molgramostim) plus sucralfate versus sucralfate alone Both groups rinsed mouth with sucralfate (1 g) suspension for 1 minute before swallowing, 6 times per day, starting after 1 week of RT and continued until the end of RT (including weekends and planned/unplanned treatment breaks). Both groups advised to rinse their mouths with saline solution in between the sucralfate rinses if required Group A: after cumulative radiation dose of 10 Gy, GM-CSF (150 µg to 300 µg - dependent on body weight) by daily subcutaneous injection until the last day of RT; not given over weekends or during planned/unplanned treatment breaks; mean total dose = 3398 µg (range 300 µg to 7200 µg) Group B: no other treatment Oral pain was treated with anti-inflammatory analgesics and with local anaesthetic mouthwashes (lidocaine hydrochloride, Xylocain 0.5%) Compliance: not reported Duration of treatment: variable and dependent on duration of RT	
Outcomes	<ul style="list-style-type: none">• Oral mucositis: 0 to 2 scale where 0 = no mucositis, 1 = erythema and edema without ulcers but food intake/use of dental prosthesis was not affected, and 2 = one or more ulcers or bleeding or food intake/use of dental prosthesis was affected (assessed weekly during RT and 1 and 6 months after completion of RT, reported at start of RT and weekly for 4 weeks after; no usable data)• Interruptions to cancer treatment (only 2 due to mucositis but not reported by group; data not usable)• Oral pain: 0 to 10 VAS and also 1 to 4 scale where 1 = no pain, 2 = mild, 3 = moderate, and 4 = severe (assessed daily at midday during RT) (data not usable - 1 to 4 scale reported as “no difference” and VAS reported on a graph with no SD or P values)• Adverse events (due to GM-CSF, sucralfate, or both)• Saliva flow rates (not an outcome of this review)• Salivary lactoferrin (not an outcome of this review)• Blood measurements (not an outcome of this review)• Body weight (not an outcome of this review)• Overall survival (not an outcome of this review)	
Notes	Sample size calculation: not reported Funding: GM-CSF and sucralfate were both provided by pharmaceutical industry (Schering-Plough Corporation and Orion-Farmos Pharmaceuticals respectively) Declarations/conflicts of interest: not reported Data handling by review authors: no usable data Other information of note: GM-CSF administration began after cumulative radiation dose of 10 Gy, by which point oral mucositis may have already begun to develop	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Makkonen 2000 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "assignment to the treatment groups was carried out via a phone call to the randomization center located at the Finnish Cancer Registry, Helsinki" Comment: use of a specialist randomisation centre
Allocation concealment (selection bias)	Low risk	Quote: "assignment to the treatment groups was carried out via a phone call to the randomization center located at the Finnish Cancer Registry, Helsinki" Comment: third party/remote randomisation would have ensured concealment of the random sequence from those recruiting participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible as no placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It would be possible to blind the outcome assessor for oral mucositis as the scale was fairly objective, but it was not mentioned. It would not be possible to blind oral pain assessment as this was done by the participant who was not blinded (however, we could not use the pain data so there was no bias for this outcome)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is not clear how many participants were included in the analyses
Selective reporting (reporting bias)	High risk	Poor reporting of oral mucositis and oral pain
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: Royal Marsden Hospital, London, UK</p> <p>Number of centres: 1</p> <p>Study duration: recruitment from September 1997 to October 2000</p> <p>Trials registry number: NCT00004256</p>
Participants	<p>Inclusion criteria: histologically proven T1 N0 or T2 N0 glottic carcinoma; due to receive RT with a 16-fraction 3-week regimen; WHO performance status 0 or 1</p> <p>Exclusion criteria: renal or hepatic impairment; serious infections requiring antibiotics; taking corticosteroids or likely to require them; known allergy to GM-CSF</p> <p>Cancer type: laryngeal</p> <p>Cancer treatment: accelerated radiotherapy: once-daily fractions of 3.125 Gy, to a total dose of 50 Gy in 16 fractions over 21 days</p> <p>Age at baseline (years): Group A: median 60 (range 48 to 79); Group B: median 65 (range 32 to 70)</p> <p>Gender: Group A: 93% male; Group B: 86% male</p> <p>Number randomised: 29 (Group A: 15; Group B: 14)</p> <p>Number evaluated: 29 (Group A: 15; Group B: 14)</p>
Interventions	<p>Comparison: GM-CSF (molgramostim) versus no treatment</p> <p>Group A: GM-CSF (150 µg) by daily subcutaneous injection, starting on day 14 of RT and continuing for 14 days i.e. for the last week of RT and for 1 week after completion of RT (total dose = 2100 µg)</p> <p>Group B: no treatment</p> <p>Compliance: 2 participants did not complete their course of GM-CSF</p> <p>Duration of treatment: 14 days</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: RTOG 0 to 4 scale (measured weekly by 1 of 2 independent observers using physician's objective criteria (see Appendix 9), reported graphically over time and by maximum score experienced in the text) (time to mucositis healing also measured but not an outcome of this review) • Normalcy of diet: use of feeding tubes • Adverse events • Analgesic use ("No differences were detected in...analgesic usage" - we do not know if this is number of days or whether or not opioids) • Dysphagia and odynophagia (not outcomes of this review) • Candida infection (not an outcome of this review) • Laryngeal edema (not an outcome of this review) • Moist or dry desquamation (not an outcome of this review) • Weight change (not an outcome of this review) • Skin erythema (not an outcome of this review)
Notes	<p>Sample size calculation: 17 per group needed at 90% power and 5% significance to detect reduction from an anticipated 60% incidence of severe mucositis to 10%</p> <p>Funding: not reported</p> <p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: N/A</p> <p>Other information of note: imbalance in stage distribution, with more T2 patients in the GM-CSF group. Consequently more of this group were treated with larger fields</p>

	GM-CSF administration only began after 14 days of radiotherapy, by which point oral mucositis may have already begun to develop	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomly assigned to the active or control arms" Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "were randomly assigned to the active or control arms" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible as no placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "At each visit one of two independent observers, blinded to group allocation, scored mucositis..." Comment: a physician's objective version of the RTOG scale was used. Use of feeding tube is also an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Analgesic use reported as "No differences" with no data, however mucositis fully reported
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (7 arms)</p> <p>Location: USA</p> <p>Number of centres: 10</p> <p>Study duration: not reported</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: 18 years or older; metastatic colon or rectal adenocarcinoma; scheduled to receive palliative 5FU and leucovorin chemotherapy; ECOG performance status 0 to 2 (ambulatory at least 50% of waking hours); life expectancy of at least 4 months; free of lesions and no recent history (within 30 days before baseline examination) of oral ulceration, herpes simplex, oral candidiasis, severe gingivitis, or the presence of active or chronic mucositis, xerostomia, or diarrhoea; absolute neutrophil count $\geq 1.5 \times 10^9/L$; platelet count $\geq 100 \times 10^9/L$; serum creatinine ≤ 2.0 mg/dL; serum bilirubin ≤ 2.0 mg/dL; serum aspartate amino transferase less than 5 times the upper limit of normal; absence of other serious concurrent medical illness</p> <p>Exclusion criteria: received chemotherapy, radiotherapy, or other investigational drugs within 4 weeks of enrolment (6 weeks for chemotherapy with mitomycin or nitrosoureas); any unresolved adverse event from previous therapy; major surgery within 2 weeks before study entry; history of insulin-dependent diabetes mellitus; pregnant or breastfeeding; of child-bearing potential and not using adequate contraceptive precautions; previous hypersensitivity reaction to leucovorin calcium or <i>Escherichia coli</i>-derived material</p> <p>Cancer type: metastatic colorectal</p> <p>Cancer treatment: (palliative) leucovorin 20 mg/m² by rapid IV injection, followed immediately by 5FU 425 mg/m² by rapid IV injection for 5 consecutive days on days 4 to 8 of each 28-day cycle</p> <p>Age at baseline (years): Group A: mean 62 (SD 10; range 44 to 84); Group B: mean 66 (SD 13; range 41 to 86)</p> <p>Gender: Group A: 57% male; Group B: 59% male</p> <p>Number randomised: 81 (Group A: 54; Group B: 27)</p> <p>Number evaluated: 81 (Group A: 54; Group B: 27)</p>
Interventions	<p>Comparison: KGF (recombinant human) versus placebo</p> <p>Group A: KGF</p> <ul style="list-style-type: none"> • (n = 7): 1 µg/kg per day by IV bolus on days 1 to 3 (total dose = 3 µg/kg) • (n = 8): 10 µg/kg as above (total dose = 30 µg/kg) • (n = 10): 20 µg/kg as above (total dose = 60 µg/kg) • (n = 11): 40 µg/kg as above (total dose = 120 µg/kg) • (n = 8): 60 µg/kg as above (total dose = 180 µg/kg) • (n = 10): 80 µg/kg as above (total dose = 240 µg/kg) <p>Group B: placebo as above</p> <p>Compliance: 3 participants stopped KGF treatment due to adverse reactions involving the skin (1 in 60 and 2 in 80 µg/kg group)</p> <p>Duration of treatment: 3 days</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale (assessed on days 1, 4, 8, 15 and 28, reported as incidence of grade 2 to 4; first cycle data only) (duration of mucositis also measured but not an outcome of this review) • Oral pain: self-assessed daily questionnaire including mouth and throat pain assessed on both a 5-point ordinal scale (reported graphically, no usable data) and a 0

	to 10 VAS (reported as AUC, not used) <ul style="list-style-type: none">Adverse events: WHO 0 to 4 scale (reported as events of any grade that differed by at least 10% between any KGF group and placebo; events were not reported if they occurred in less than 10% of KGF group; also reported as incidence of grade 3 to 4 events)Blood measurements (not an outcome of this review)	
Notes	Sample size calculation: not reported Funding: “Supported by a grant from Amgen, Inc” (pharmaceutical industry) Declarations/conflicts of interest: not reported Data handling by review authors: we combined the 6 KGF groups to make a single pairwise comparison against placebo; in order to make a head-to-head comparison of doses we grouped the 3 lower doses (1 µg/kg, 10 µg/kg and 20 µg/kg) together and grouped the 3 higher doses (40 µg/kg, 60 µg/kg and 80 µg/kg) together to make pairwise groups for comparison Other information of note: not reported	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “This study was a multicenter, randomized, double-blinded, placebo-controlled, phase I study” Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: “This study was a multicenter, randomized, double-blinded, placebo-controlled, phase I study” Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double-blinded, placebo-controlled” Comment: the use of a placebo should have ensured that blinding was successful; incidence of adverse events does not appear to differ enough between groups to cause unblinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double-blinded, placebo-controlled” Comment: it is not clear who was blinded but the outcome is grade 2 to 4 WHO-scale

Meropol 2003 (Continued)

		mucositis and it is unlikely that this would be affected by any lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Nemunaitis 1995

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: USA and Canada</p> <p>Number of centres: 7</p> <p>Study duration: 1 November 1990 to 1 July 1993</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: any age; undergoing allogeneic BMT (from HLA-identical sibling) for haematological malignancy</p> <p>Exclusion criteria: due to receive methotrexate as part of GVHD prophylaxis; chronic lymphocytic leukaemia; chronic myelogenous leukaemia in blast crisis; acute lymphoblastic leukaemia or acute myelogenous leukaemia with failure at first induction or progressed beyond a second relapse; previously received cytokines; HIV; life expectancy less than 7 days</p> <p>Cancer type: haematologic malignancy: lymphoid malignancy (Group A: 21%; Group B: 16%); acute myeloid malignancy (Group A: 34%; Group B: 27%); chronic myeloid malignancy (Group A: 32%; Group B: 30%); multiple myeloma (Group A: 6%; Group B: 5%); myelodysplastic syndrome (Group A: 6%; Group B: 11%); aplastic anaemia (Group A: 2%; Group B: 11%)</p> <p>Cancer treatment: prior to receiving allogeneic BMT (from HLA-identical sibling), participants received the following conditioning regimens: busulfan and cyclophosphamide with TBI (Group A: 9%; Group B: 16%) or without TBI (Group A: 32%; Group B: 34%); busulfan, cyclophosphamide, cytosine arabinoside, and methotrexate with TBI (Group A: 23%; Group B: 13%) or without TBI (Group A: 8%; Group B: 11%); cyclophosphamide and steroid with TBI (Group A: 0%; Group B: 2%); cyclophosphamide, cytosine arabinoside, and steroid with TBI (Group A: 23%; Group B: 18%); etoposide with TBI (Group A: 0%; Group B: 2%); etoposide, cytosine arabinoside, and cyclophosphamide with TBI (Group A: 2%; Group B: 0%); etoposide, cytosine arabinoside, cyclophosphamide, and asparaginase with TBI (Group A: 0%; Group B: 2%); etoposide, methotrexate, cytosine arabinoside, and steroid with TBI (Group A: 4%; Group B: 4%)</p> <p>All participants received cyclosporine and methylprednisolone for GVHD prophylaxis</p> <p>Age at baseline (years): Group A: mean 32; Group B: mean 34</p> <p>Gender: Group A: 60% male; Group B: 54% male</p> <p>Number randomised: 109 (Group A: 53; Group B: 56)</p> <p>Number evaluated: 109 (Group A: 53; Group B: 56)</p>

Interventions	Comparison: GM-CSF (yeast-derived recombinant human) versus placebo Group A: GM-CSF (250 µg/m ²) by 4-hour IV infusion starting on day 0 (the day of BMT) to day 20 (total dose = 5250 µg/m ²) Group B: as above with placebo Compliance: Group A: 13 participants (25%) stopped their intervention early: 11 due to adverse events (1 rash, 7 bone pain, 2 acute dyspnoea, 1 seizure); 2 (with no apparent toxicity) due to participant or physician request; Group B: 9 participants (16%) stopped their intervention early: 6 due to adverse events (2 rash, 2 bone pain, 1 elevated liver enzymes, 1 infections); 2 (on day 19) due to miscalculation of the number of days to receive the intervention; 1 (on day 9) due to severe mucositis and veno-occlusive disease of the liver Duration of treatment: 21 days	
Outcomes	<ul style="list-style-type: none">• Oral mucositis: assessment methods are not clear but reported on 0 to 4 scale which is probably WHO (assessment frequency and duration also unclear, reported in text as incidence of grade 2 to 4 and grade 3 to 4)• Adverse events: 0 to 4 scale which is probably WHO (reported as incidence of any grade of event and incidence of grade 3 to 4 events with a greater than 10% frequency)• Number of days in hospital (reported as median values; unable to use data)• GVHD incidence and severity (not an outcome of this review)• Veno-occlusive disease of the liver (not an outcome of this review)• Blood measurements (not an outcome of this review)• Infection: bacterial, fungal and viral (not an outcome of this review)• Duration of IV antibiotics (not an outcome of this review)• Fever (not an outcome of this review)• Survival: overall, disease-free, relapse (not an outcome of this review)	
Notes	Sample size calculation: not reported Funding: “..product provided by Immunex” (pharmaceutical). Also mention of “sponsoring company” which is likely to be Immunex Declarations/conflicts of interest: not reported but 4 authors employed by Immunex Data handling by review authors: N/A Other information of note: GM-CSF administration only began after the conditioning regimen, by which point oral mucositis may have already begun to develop	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Assignment to treatment was made via a randomization schema prepared by Almedica Corporation” Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: “Blinded numbered vials containing placebo or rhGM-CSF were provided

Nemunaitis 1995 (Continued)

		to each participating centre. The pharmacists, principal investigators, patients, support care personnel and sponsoring company were blinded to the study medication for the entire course of the study” Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double-blind placebo-controlled” and “The pharmacists, principal investigators, patients, support care personnel and sponsoring company were blinded to the study medication for the entire course of the study” Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double-blind placebo-controlled” and “The pharmacists, principal investigators, patients, support care personnel and sponsoring company were blinded to the study medication for the entire course of the study” Comment: everyone involved in the study was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	5 participants in the placebo group received cytokines off study during the first 42 days after BMT but unlikely to bias the results in a meaningful way

Peterson 2009

Methods	Trial design: parallel (3 arms) Location: Russia Number of centres: 9 Study duration: recruitment from August 2006 to May 2007 Trials registry number: none/unknown
Participants	Inclusion criteria: 18 years or older with colorectal cancer (stage I to IV); undergoing chemotherapy as primary cancer therapy; experienced WHO grade 2 or higher oral mucositis during first cycle of chemotherapy, but recovered prior to enrolment (i.e. grade 0); ECOG score of 0 to 2

	<p>Exclusion criteria: pregnant (or risk of pregnancy) or lactating; scheduled to receive RT to the head and neck; received other investigational drugs within 14 days of the start of the study; evidence of alcohol and drug abuse; pre-existing conditions such as active fungal or herpetic infection</p> <p>Cancer type: colorectal (stage I to IV)</p> <p>Cancer treatment: all participants received 5FU (97% with leucovorin) but 1 received capecitabine; 6 participants (3 in low-dose ITF, 3 in placebo) also received oxaliplatin; doses or regimens comparable between groups</p> <p>Age at baseline (years): Group A: median 62 ; Group B: median 56 ; Group C: median 59</p> <p>Gender: Group A: 42% male; Group B: 33% male; Group C: 48% male</p> <p>Number randomised: 99 (Group A: 33; Group B: 33; Group C: 33)</p> <p>Number evaluated: 99 (Group A: 33; Group B: 33; Group C: 33)</p>	
Interventions	<p>Comparison: ITF (recombinant human) versus placebo</p> <p>Group A: ITF (10 mg/mL) oral spray, 300 µL (3 sprays) to the oral mucosa 8 times daily, starting on the first day (day 1) of the second chemotherapy cycle for total 14 days (total dose = 336 mg)</p> <p>Group B: ITF (80 mg/mL) oral spray as above (total dose = 2688 mg)</p> <p>Group C: placebo oral spray as above</p> <p>Compliance: patient-reported compliance was 97%</p> <p>Duration of treatment: 14 days</p>	
Outcomes	<ul style="list-style-type: none">• Oral mucositis: WHO 0 to 4 scale (assessed on days 0, 1, 3, 5, 7, 10, 12, 14, and 21 ± 2, maximum score reported) (duration of mucositis also measured but not an outcome of this review)• Oral mucositis: OMAS 0 to 45 scale (assessed on days reported above; WHO data used for analysis)• Adverse events (assessed on days reported above)• Patient daily self-assessment: including discolouration, mouth and throat pain, preference for solid/semi-solid food, analgesic use, and dysphagia (no usable data for the outcomes relevant to this review)	
Notes	<p>Sample size calculation: based on previous study, 80% power to detect 40% difference in incidence of WHO grade 2 or above</p> <p>Funding: The GI Company (pharmaceutical)</p> <p>Declarations/conflicts of interest: some authors had roles with the funding pharmaceutical company (and other companies) both compensated and uncompensated</p> <p>Data handling by review authors: we combined the 2 ITF groups to make a single pairwise comparison against placebo; we also made a separate comparison of the 2 ITF dosages</p> <p>Other information of note: not reported</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Peterson 2009 (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned" Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly assigned" Comment: insufficient information to determine whether or not the random sequence was adequately concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" Comment: it is not clear who was blinded. There are subjective elements to the assessment of oral mucositis using this scale, requiring the patient's assessment of pain/soreness and their ability to swallow but, as the participants were unaware of their group allocation, the assessment of oral mucositis can be considered to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Rosen 2006

Methods	Trial design: parallel (2 arms) Location: USA and Australia Number of centres: 15 Study duration: not reported Trials registry number: none/unknown
Participants	Inclusion criteria: 18 years or older with advanced (Duke's D) colon or rectal adenocarcinoma; scheduled to receive bolus 5FU and low-dose leucovorin (Mayo regimen) as first-line or subsequent therapy; normal oral cavity examination (no ulceration, herpes simplex, candidiasis, or severe gingivitis); ECOG score of 0 to 2; life expectancy of 4 months or more; absolute neutrophil count of 1.5×10^9 /L or higher; platelet count of 100×10^9 /L or higher

	<p>° /L or higher; normal renal and hepatic function</p> <p>Exclusion criteria: previous radiotherapy or chemotherapy within 4 weeks or major surgery within 2 weeks of study day 1; insulin-dependant diabetes; known allergy to leucovorin; known hypersensitivity to <i>Escherichia coli</i>-derived material</p> <p>Cancer type: advanced colorectal (Duke's D)</p> <p>Cancer treatment: low-dose leucovorin (20 mg/m²) by IV immediately followed by 5FU (425 mg/m²) by rapid IV once daily for 5 consecutive days on days 4 to 8 of each 28-day cycle; 2 cycles (5FU dose could be decreased by 20% during cycle 2 if moderately severe toxicities occurred in cycle 1)</p> <p>Age at baseline (years): Group A: mean 65 (SD 11.2); Group B: mean 65 (SD 11.1)</p> <p>Gender: Group A: 57% male; Group B: 72% male</p> <p>Number randomised: 65 (not reported by group)</p> <p>Number evaluated: 64 (Group A: 28; Group B: 36)</p>	
Interventions	<p>Comparison: KGF (palifermin) versus placebo</p> <p>Group A: KGF (40 µg/kg) by IV for 3 consecutive days (days 1 to 3 of each 28-day cycle) before the start of chemotherapy (total dose = 120 µg/kg)</p> <p>Group B: as above with placebo</p> <p>Compliance: not reported (only reports “palifermin was generally well tolerated”)</p> <p>Duration of treatment: 3 days</p>	
Outcomes	<ul style="list-style-type: none">• Oral mucositis: WHO 0 to 4 scale (assessed on days 0, 1, 4, 8, 12, 15, and 28, maximum score reported)• Oral pain: patient daily self-assessment using OMDQ 5-point scale for mouth and throat soreness (higher = worse pain, reported as AUC, not used)• Adverse events• Diarrhoea (related to the cancer therapy - not an outcome of this review)• Laboratory assessments (not an outcome of this review)• Neutropenia (not an outcome of this review)• Antibody assessments (not an outcome of this review)• Survival (not an outcome of this review)	
Notes	<p>Sample size calculation: not reported</p> <p>Funding: “Supported by Amgen Inc” (pharmaceutical industry)</p> <p>Declarations/conflicts of interest: all authors were linked to the funding pharmaceutical company in terms of employment, consultancy, stock ownership, honoraria, and receipt of research funding</p> <p>Data handling by review authors: data were reported separately for the chemotherapy cycles 1 and 2 - we used the data for cycle 1</p> <p>Other information of note: not reported</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Patients were randomly assigned (by center and prior chemotherapy)” Comment: insufficient information to determine method of random sequence gen-

Rosen 2006 (Continued)

		eration
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly assigned (by center and prior chemotherapy)" Comment: insufficient information to determine method of random sequence generation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" Comment: it is not clear who was blinded. There are subjective elements to the assessment of oral mucositis using this scale, requiring the patient's assessment of pain/soreness and their ability to swallow but, as the participants were unaware of their group allocation, the assessment of oral mucositis can be considered to be blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 randomised participant was not included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

SaariLahti 2002

Methods	Trial design: parallel (2 arms) Location: Helsinki University Central Hospital, Finland Number of centres: 1 Study duration: recruitment from October 1999 to April 2001 Trials registry number: none/unknown
Participants	Inclusion criteria: undergone radical surgery for head and neck cancer and scheduled to receive postoperative RT to a total dose of 50 Gy or more to the oral and oropharyngeal mucosa Exclusion criteria: prior chemotherapy or RT; chronic autoimmune or inflammatory disease; WHO performance score > 2 Cancer type: head and neck: mobile tongue (Group A: 33%; Group B: 37%); floor of mouth (Group A: 19%; Group B: 16%); tonsil (Group A: 29%; Group B: 32%); oral cavity other (Group A: 19%; Group B: 16%) Cancer treatment: mean time from radical surgery to start of RT: Group A: 39 days (range 20 to 73); Group B: 38 days (range 20 to 56); conventionally fractionated RT to a total dose of 50 Gy to 60 Gy in 2-Gy daily fractions, 5 times weekly (on weekdays) for

	<p>5 to 6 weeks, to the primary site and locoregional lymph nodes</p> <p>Age at baseline (years): Group A: median 56 (range 43 to 87); Group B: median 60 (range 24 to 72)</p> <p>Gender: Group A: 57% male; Group B: 79% male</p> <p>Number randomised: 40 (Group A: 21; Group B: 19)</p> <p>Number evaluated: 40 (Group A: 21; Group B: 19)</p>
Interventions	<p>Comparison: GM-CSF versus sucralfate</p> <p>Group A: starting after a cumulative RT dose of 10 Gy (after 1 week of RT); mouth was cleaned with water, then GM-CSF (37.5 µg per 25 mL rinse) mouthwash rinsed around the mouth for 3 minutes then swallowed, 4 times daily after meals, on RT-days (weekdays), until the end of RT (total dose dependent on duration of RT)</p> <p>Group B: as above but with sucralfate (1 g per 25 mL rinse) (total dose dependent on duration of RT)</p> <p>Compliance: not reported (only reports “both mouthwashes were well tolerated, and none of the patients reported any adverse effects related to the mouthwashes”)</p> <p>Duration of treatment: 4 to 5 weeks (dependent on duration of RT)</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: RTOG 0 to 4 scale (assessed before RT, weekly during RT, and at 1, 2, and 4 weeks after RT, reported graphically as mean score over time but authors provided maximum incidence data on request) <ul style="list-style-type: none"> • Interruptions to cancer treatment (RT interruptions due to OM) • Oral pain: 0 (no pain) to 10 (worse pain) VAS (assessed as reported above, reported graphically as mean score over time - no mean maximum score and no SDs, unable to use data) <ul style="list-style-type: none"> • Normalcy of diet: use of PEG feeding tube • Adverse events • Incidence of hospitalisation (number of days in hospital is an outcome of this review and therefore we did not use these data) • Opioid analgesic use (reported as incidence; number of days of treatment with opioid analgesics is an outcome of this review and therefore we did not use these data) • Laboratory parameters (not outcomes of this review) • Use of antimycotic agents (not an outcome of this review) • Use of antibiotics (not an outcome of this review) • Weight loss (not outcomes of this review)
Notes	<p>Sample size calculation: not reported</p> <p>Funding: not reported</p> <p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: we used oral mucositis incidence (maximum score experienced per patient) data provided by the authors; all participants experienced mucositis (grade 1 or above) as they had already received a week of RT before the intervention started, therefore we felt an analysis of incidence of any grade of mucositis should not be included</p> <p>Other information of note: GM-CSF/sucralfate administration only began after 1 week of RT, by which point oral mucositis may have already begun to develop</p>
<i>Risk of bias</i>	

Saarihahti 2002 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done using computer-generated random digits" Comment: adequate method used
Allocation concealment (selection bias)	Low risk	Quote: "they were assigned to a treatment group by way of a telephone call to the randomization office" Comment: third party/remote randomisation would have ensured concealment of the random sequence from those recruiting participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind" and "Both solutions looked alike, and neither the investigators nor the patients were aware of the contents of the solutions given. The drug vials were marked with a study code that prevented identification of the allocation group" Comment: adequate methods to ensure blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blinded, placebo-controlled" Comment: nobody involved in the study was aware of group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Schneider 1999

Methods	Trial design: parallel (2 arms) Location: USA Number of centres: not reported Study duration: recruitment from January 1995 to April 1996 Trials registry number: none/unknown
Participants	Inclusion criteria: 18 years or older with histologically proven head and neck malignancy; mucosa of the oropharynx and/or oral cavity to be included in RT portal; Karnofsky performance score of 60 or more; no known hypersensitivity to <i>E coli</i> -derived

	<p>proteins; haemoglobin and platelet counts 100×10^9 /L or higher; absolute neutrophil count higher than 1.5×10^9 /L; normal blood pressure; agreement to bring dentition to acceptable level prior to RT (teeth with periapical abscesses or severe periodontal disease extracted, followed by a 10-day healing period allowance)</p> <p>Exclusion criteria: lactating/pregnant/females not taking effective form of contraception; scheduled to receive chemotherapy or radiosensitising drugs during the planned RT; history of myeloid malignancy; underlying collagen vascular disease; active rheumatoid arthritis</p> <p>Cancer type: head and neck: nasopharynx (Group A: 0; Group B: 1); oropharynx (Group A: 2; Group B: 1); tongue (Group A: 2; Group B: 1); larynx (Group A: 2; Group B: 1); other/unknown (Group A: 2; Group B: 2)</p> <p>Cancer treatment: radiotherapy in 1.8 Gy to 2 Gy standard daily fractions from Monday to Friday, to total dose 50 Gy or more</p> <p>Age at baseline (years): not reported</p> <p>Gender: Group A: 100% male; Group B: 83% male</p> <p>Number randomised: 14 (Group A: 8; Group B: 6)</p> <p>Number evaluated: 14 (Group A: 8; Group B: 6)</p>	
Interventions	<p>Comparison: G-CSF (r-metHuG-CSF) (filgrastim) versus placebo</p> <p>Group A: G-CSF (starting at 3 µg/kg and titrated to keep neutrophil count between 10×10^9 /L and 30×10^9 /L) by daily subcutaneous injection, starting on the first day of RT (weekdays), until the end of RT (total dose dependent on duration of RT and neutrophil counts)</p> <p>Group B: placebo as above</p> <p>Compliance: not reported (only reports “Filgrastim was well tolerated”)</p> <p>Duration of treatment: variable and dependent on duration of RT</p>	
Outcomes	<ul style="list-style-type: none">• Oral mucositis: WHO 0 to 4 scale (assessed on weekly by single examiner, reported as incidence of any mucositis and grade 3 or higher)• Oral mucositis: Hickey 0 to 3 scale (not used)• Interruptions to cancer treatment (delays or dose reductions, no usable data)• Weight change (not an outcome of this review)• Blood measurements (not an outcome of this review)	
Notes	<p>Sample size calculation: 54 required to detect 30% decrease in incidence of grade 2 or 3 mucositis at 80% power at the 5% significance level</p> <p>Funding: “Financial support was provided through a grant from Amgen Inc” (pharmaceutical industry)</p> <p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: interruptions to cancer treatment outcome only reported narratively</p> <p>Other information of note: study was stopped after an interim analysis. Authors state that “owing to administrative obstacles, completion of the trial is not possible”, rather than due to previously stated early stopping rules</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote: "The patients were randomized equally between the two treatment groups" and "The study material and randomization list were held by the UCLA Pharmacy for the duration of the study" Comment: method of random sequence generation not described but done by UCLA Pharmacy and therefore probably done adequately
Allocation concealment (selection bias)	Low risk	Quote: "Amgen Inc...prepared and packaged all drug and placebo in identical containers, with the only designator being the randomization number. The study material and randomization list were held by the UCLA Pharmacy for the duration of the study" Comment: pharmacy-controlled randomisation would have ensured concealment of the random sequence from those recruiting participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" and "Amgen Inc...prepared and packaged all drug and placebo in identical containers, with the only designator being the randomization number" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind, placebo-controlled" and "A single examiner...who was blinded to the patients' randomization status...scored mucositis on a weekly basis" Comment: both participants and outcome assessor were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	Although the study reports an interim analysis only, the study was stopped due to administrative reasons and is unlikely to introduce bias

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: USA</p> <p>Number of centres: 13</p> <p>Study duration: recruitment from March 2001 to October 2002</p> <p>Trials registry number: NCT00041665</p>
Participants	<p>Inclusion criteria: 18 years or older; Karnofsky performance score of 70 or more; scheduled to undergo autologous HSCT after conditioning regimen of fractionated TBI plus etoposide and cyclophosphamide for haematological cancers; adequate cardiac, pulmonary, renal, and hepatic function</p> <p>Exclusion criteria: not reported</p> <p>Cancer type: haematologic: NHL (Group A: 68%; Group B: 65%); Hodgkins (Group A: 20%; Group B: 22%); multiple myeloma (Group A: 10%; Group B: 8%); leukaemia (Group A: 2%; Group B: 5%)</p> <p>Cancer treatment: prior to autologous HSCT, participants received the following conditioning regimen:</p> <ul style="list-style-type: none"> • Radiotherapy: prior to chemotherapy, TBI of total 12 Gy in 6, 8, or 10 fractions over 3 or 4 days, with at least 6 hours between fractions • Chemotherapy: IV etoposide (60 mg/kg) the day after the last RT fraction (4 days before HSCT) and cyclophosphamide (100 mg/kg) 2 days later (2 days before HSCT) <p>All participants received G-CSF (filgrastim) 5 µg/kg per day from HSCT until neutrophil recovery</p> <p>Age at baseline (years): Group A: median 48 (range 18 to 69); Group B: median 49 (range 19 to 68)</p> <p>Gender: Group A: 56% male; Group B: 68% male</p> <p>Number randomised: 214 (Group A: 107; Group B: 107)</p> <p>Number evaluated: 212 (Group A: 106; Group B: 106)</p>
Interventions	<p>Comparison: KGF (palifermin) versus placebo</p> <p>Group A: KGF (60 µg/kg) by IV for 3 consecutive days starting 3 days before RT, followed by 3 more doses after HSCT starting on the day of HSCT (total dose = 360 µg/kg)</p> <p>Group B: placebo as above</p> <p>Compliance: 212 participants received at least 1 dose of their allocated intervention and 205 participants (Group A: 103; Group B: 102) “completed the study” (it is not clear whether or not this means that they received all doses)</p> <p>Duration of treatment: 6 treatment days over 13 to 14 days</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale (assessed daily by trained assessors starting 8 days before HSCT and for 28 days after HSCT or until severe mucositis had returned to grade 0 to 2, maximum score reported) (duration of grade 3 to 4 oral mucositis also measured but not an outcome of this review) • Oral mucositis: RTOG 0 to 4 scale (assessed as above but only used for reporting duration of severe mucositis) • Oral mucositis: WCCNR 0 to 3 scale (assessed as above but only used for reporting duration of severe mucositis) • Oral pain: patient daily self-assessment (day -12 to 28) using OMDQ 5-point scale for mouth and throat soreness (higher = worse pain, reported as AUC, not used) • Quality of life: physical, functional, emotional, and social/family well-being

	domains of the FACT general questionnaire (days -12, -1, 7, 10, 14, and 28, reported as AUC, not used) <ul style="list-style-type: none">• Normalcy of diet (measured as incidence of TPN)• Adverse events: 1 (mild) to 5 (fatal) scale• Number of days of treatment with opioid analgesics (reported as median and range, unable to use data)• Dysphagia (not an outcome of this review)• Febrile neutropenia (not an outcome of this review)• Infections (not an outcome of this review)• Survival (not an outcome of this review)• Laboratory results (not an outcome of this review)	
Notes	Sample size calculation: 210 participants required to detect a mean difference in duration of severe oral mucositis of at least 3 days (SD 6.6) at 90% power and 5% significance Funding: “Funded by Amgen” (pharmaceutical industry) Declarations/conflicts of interest: the majority of authors were linked to the funding pharmaceutical company in terms of employment, consulting fees, lecture fees, receipt of research funding, and ownership of equity Data handling by review authors: N/A Other information of note: not reported	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “patients were randomly assigned in a 1:1 ratio” Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: “patients were randomly assigned in a 1:1 ratio” Comment: insufficient information to determine method of random sequence generation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “placebo-controlled, double-blind” Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “placebo-controlled, double-blind” Comment: it is not clear who was blinded. There are subjective elements to the assessment of lower grades of oral mucositis using the WHO scale, requiring the patient’s assessment of pain/soreness and their ability to swallow. Higher grades have more objective elements so may not be affected by

		potential lack of blinding of the assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 randomised participants (1 per group) were not included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Su 2006

Methods	Trial design: parallel (2 arms) Location: USA Number of centres: 1 Study duration: recruitment from January 1992 to December 1996 Trials registry number: none/unknown
Participants	Inclusion criteria: 18 years or older with histologically proven AJCC stage II to IV squamous cell carcinoma of the head and neck; undergone gross complete resection with negative pathological surgical margins and medically fit to begin RT within 8 weeks of surgery; Karnofsky performance score of 80% or more; adequate haematologic and serum metabolic laboratory indices Exclusion criteria: nasopharyngeal cancer; concurrent active malignancy other than localised; nonmelanoma skin cancer; previous RT to head and neck; previous chemotherapy; positive serum β -human chorionic gonadotropin in women of procreative potential; need for tube feeding at the start of RT Cancer type: stage II to IV squamous cell carcinoma of the head and neck: hypopharynx (Group A: 11%; Group B: 5%); larynx (Group A: 16%; Group B: 23%); oral cavity (Group A: 26%; Group B: 27%); oropharynx (Group A: 21%; Group B: 32%); unknown primary (Group A: 26%; Group B: 14%) Cancer treatment: postoperative external beam RT in once-daily fractions of 1.8 Gy, 5 days per week, to total dose of 63 Gy at primary site and involved neck (54 Gy to regional lymphatics at risk for subclinical metastasis; spinal cord dose limited to 45 Gy) Age at baseline (years): Group A: median 67 (interquartile range 59 to 75); Group B: median 61 (interquartile range 54 to 67) Gender: Group A: 79% male; Group B: 73% male Number randomised: 41 (Group A: 19; Group B: 22) Number evaluated: 40 (Group A: 19; Group B: 21)
Interventions	Comparison: G-CSF versus placebo Group A: G-CSF (3 μ g/kg) by daily subcutaneous injection, 7 days per week, starting 3 days before the start of RT and continued to end of RT (total dose = dependent on duration of RT) Group B: placebo as above Compliance: not reported Duration of treatment: variable and dependent on duration of RT

Outcomes	<ul style="list-style-type: none"> • Oral mucositis: unknown 0 to 3 scale, where 0 = none, 1 = erythema, 2 = patchy mucositis, and 3 = confluent mucositis (assessed twice weekly by the treating radiation oncologist, maximum score reported) • Interruptions to cancer treatment: RT interruptions • Normalcy of diet (use of PEG feeding tube, as defined by 10% or higher weight loss from pre-RT baseline) • Adverse events (NCI-CTC) • Blood measurements (not an outcome of this review) • Survival (not an outcome of this review)
Notes	<p>Sample size calculation: planned sample size was 66 per group to detect absolute difference of 20% in PEG tube use (from 10% in one group to 30% in the other) at 80% power and 5% significance</p> <p>Funding: “This study was supported by NIH grant #CA69913” (government)</p> <p>Declarations/conflicts of interest: “No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this article”</p> <p>Data handling by review authors: although the scale for assessing oral mucositis does not completely match the 0 to 4 scales (such as WHO, etc), it was possible to dichotomise it for use in the ‘any mucositis’ meta-analysis, and we also used grade 3 (confluent mucositis) as incidence of severe mucositis</p> <p>Other information of note: planned to enrol 132 participants but stopped due to slow recruitment</p>

Risk of bias

Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients were randomized...by randomly permuted blocks...A randomization list was prepared by the Memorial Sloan-Kettering Cancer Center Biostatistics Service and held by the pharmacy” Comment: specialist centre used
Allocation concealment (selection bias)	Low risk	Quote: “A randomization list was prepared by the Memorial Sloan-Kettering Cancer Center Biostatistics Service and held by the pharmacy. Investigators did not have access to this list, ensuring that allocation could not be predicted before registration or changed afterwards” Comment: central/remote randomisation would have ensured concealment of the random sequence from those recruiting participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double-blind, placebo-controlled” and “All patients and treating physicians were blinded to treatment group assign-

Su 2006 (Continued)

		ment” Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double-blind, placebo-controlled” and “All patients and treating physicians were blinded to treatment group assignment” Comment: the treating physician was the outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 randomised participant was not included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Vadhan-Raj 2010

Methods	<p>Trial design: parallel (2 arms)</p> <p>Location: University of Texas MD Anderson Cancer Center, USA</p> <p>Number of centres: 1</p> <p>Study duration: recruitment from December 2005 to February 2008; last follow-up in May 2008</p> <p>Trials registry number: NCT00267046 (mentioned in trial report)</p>
Participants	<p>Inclusion criteria: aged 15 to 65 years with sarcoma; due to start chemotherapy at the centre; Karnofsky performance score of 80% or more; adequate bone marrow, renal, and hepatic function</p> <p>Exclusion criteria: history of pelvic RT; clinically significant cardiac disease; undergone surgery within the previous 2 weeks</p> <p>Cancer type: sarcoma</p> <p>Cancer treatment: doxorubicin (total dosage 90 mg/m²) administered by continuous IV infusion over 72 hours, and ifosfamide (total dosage 10 g/m²) administered by 3-hour IV infusion for 4 days; participants with osteosarcoma (Group A: 2; Group B: 1) received the same dosage of doxorubicin but with intra-arterial cisplatin (120 mg/m²); all participants received G-CSF (pegfilgrastim) the day after chemotherapy; cycle repeated every 21 days; planned 6 cycles</p> <p>Age at baseline (years): Group A: median 42 (range 17 to 63); Group B: median 39 (range 15 to 64)</p> <p>Gender: Group A: 53% male; Group B: 50% male</p> <p>Number randomised: 48 (Group A: 32; Group B: 16)</p> <p>Number evaluated: 48 (Group A: 32; Group B: 16)</p>

Interventions	Comparison: KGF (palifermin) versus placebo Group A: KGF (180 µg/kg) by IV as single dose 3 days before the start of each chemotherapy cycle Group B: placebo as above Compliance: the proportion of participants that completed all 6 blinded cycles (i.e. they took their allocated intervention) was higher in Group A (63%) than Group B (31%) Duration of treatment: 1 day per 3-week cycle; planned total 6 days of intervention over 18 weeks	
Outcomes	<ul style="list-style-type: none">• Oral mucositis: WHO 0 to 4 scale (assessed for each cycle before chemotherapy, days 10, 12, 14 and at the end of the cycle, reported as incidence of grade 2 to 4 and grade 3 to 4, reported separately for blinded phase (first 2 cycles) and then the open-label phase) (duration of mucositis also measured but not an outcome of this review)• Oral pain: 0 to 10 (10 being worst) scale (assessed by questionnaire for each cycle before chemotherapy, days 10, 12, 14 and at the end of the cycle, reported for blinded phase, reported as median maximum score; unable to use data)• Quality of life: 1 to 7 (7 being worst) scale (assessed by questionnaire for each cycle before chemotherapy, days 10, 12, 14 and at the end of the cycle, reported for blinded phase, reported as median maximum score; unable to use data)• Normalcy of diet: eating and drinking assessed separately on 0 to 4 (4 being most difficult) scales (assessed by questionnaire for each cycle before chemotherapy, days 10, 12, 14 and at the end of the cycle, reported for blinded phase, reported as median maximum score; unable to use data)• Adverse events• Opioid analgesic use (reported as quantity per cycle; number of days of treatment with opioid analgesics is an outcome of this review and therefore we did not use these data)• Multiple patient-reported outcomes (overall health, sleeping, dysphagia, talking, brushing teeth, throat pain, rectal soreness) (not outcomes of this review)• Blood and laboratory measurements (not outcomes of this review)• Weight loss (not an outcome of this review)• Survival (not an outcome of this review)	
Notes	Sample size calculation: 48 participants required to detect absolute difference of 50% (from 26% in Group A to 76% in Group B) in grade 2 to 4 mucositis at 88% power and 5% significance Funding: “Amgen provided the palifermin and partial funding for the study” (pharmaceutical industry) Declarations/conflicts of interest: principal investigator is a member of the Amgen board Data handling by review authors: we only report data from the first 2 cycles (blinded phase) as very few participants received placebo in the remaining cycles Other information of note: not reported	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	<p>Quote: “Two distinct computer-generated randomization lists were prepared by the University of Texas M.D. Anderson Cancer Center, Department of Biostatistics, one for the 20 patients who consented to pharmacokinetic sampling and the other for the 28 patients who did not. For the pharmacokinetics cohort, the treatment allocation ratio was 4 patients receiving palifermin to 1 receiving placebo, in blocks of 5; for the other cohort, the ratio was 4 patients receiving palifermin to 3 receiving placebo, in blocks of 14”</p> <p>Comment: adequate method used</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: “The statistician provided both randomization lists to the pharmacy, so the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment. At patient enrolment, the research team notified the pharmacy, which assigned the patient the next sequential slot and treatment from the appropriate randomization list on the basis of whether he or she had consented to pharmacokinetic sampling. The pharmacy provided the research team with the blinded study medication. Upon completion of the study, pharmacy provided the statistician with the 2 randomization lists, including individual patient treatment assignments, for analysis”</p> <p>Comment: pharmacy-controlled randomisation would have ensured concealment of the random sequence from those recruiting participants</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: “double-blind, placebo-controlled” and “the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment” and “Blinding might not have been maintained because of adverse effects of palifermin”</p> <p>Comment: some personnel may not have been blinded due to increased adverse effects, although adverse effects from palifermin may have been difficult to isolate from adverse effects of cancer treatment</p>

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double-blind, placebo-controlled” and “the patient and the clinical research team (who assessed outcomes) were blinded to the study treatment” and “Blinding might not have been maintained because of adverse effects of palifermin” and “patients were assessed at each cycle by both research and clinical teams, including those without direct knowledge of the protocol” Comment: it seems unlikely that lack of blinding would affect outcomes as the higher grades of oral mucositis assessed in this study are more objective; also, some were assessed by personnel without knowledge of the protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

van der Lelie 2001

Methods	Trial design: parallel (2 arms) Location: the Netherlands Number of centres: 1 Study duration: recruitment from May 1997 to August 1999 Trials registry number: none/unknown
Participants	Inclusion criteria: malignant disease and due to have myeloablative treatment followed by autologous or allogeneic BMT or PBSCT Exclusion criteria: not reported Cancer type: haematologic: lymphoma (Group A: 28%; Group B: 50%); acute leukaemia (Group A: 28%; Group B: 28%); CML (Group A: 22%; Group B: 6%); multiple myeloma (Group A: 22%; Group B: 17%) Cancer treatment: prior to autologous or allogeneic BMT or PBSCT, participants received the following conditioning regimens: <ul style="list-style-type: none"> • BEAM (Group A: 28%; Group B: 44%): carmustine (BCNU) 300 mg/m² on day -6; etoposide (VP16) and cytosine arabinoside (Ara-C) 200 mg/m² of each on days -5, -4, -3, -2; melphalan 140 mg/m² on day -1 • CYTBI (Group A: 56%; Group B: 44%): cyclophosphamide 60 mg/kg on days -5 and -4; TBI 4.5 Gy on days -2 and -1 • BUCY (Group A: 17%; Group B: 11%): busulfan 4 mg/kg on days -7, -6, -5, -4; cyclophosphamide 60 mg/kg on days -3 and -2 Lymphoma patients received BEAM; other patients received CYTBI or BUCY; nearly

	<p>all participants received autologous or allogeneic PBSCT</p> <p>Age at baseline (years): Group A: median 47 (range 25 to 63); Group B: median 48 (range 18 to 62)</p> <p>Gender: Group A: 61% male; Group B: 39% male</p> <p>Number randomised: 36 (Group A: 18; Group B: 18)</p> <p>Number evaluated: 36 (Group A: 18; Group B: 18)</p>
Interventions	<p>Comparison: GM-CSF versus placebo</p> <p>Group A: GM-CSF (300 µg daily dose) gel, 5 mL twice daily (early in the morning and before going to sleep) kept in the mouth for as long as possible and then swallowed; no oral intake for 1 hour afterwards; starting on day 1 (the day after the day of transplant) and continued until neutrophil recovery (typically up to 14 days after transplant)</p> <p>Group B: placebo as above</p> <p>All participants followed hospital's standard protocol for mouth care: toothbrushing after meals, rinsing with 0.9% saline, and if there was inflammation, 0.12% chlorhexidine rinse 6 times daily</p> <p>Compliance: 8 participants (Group A: 4; Group B: 4) did not complete the study; they all cited the main reason being nausea and the taste of the gel</p> <p>Duration of treatment: variable and dependent on neutrophil recovery</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale (assessed daily by dentists, reported in text as incidence of grade 3 to 4) • Oral mucositis: 8 (all 8 sites normal) to 24 (all 8 sites severely affected) oral assessment score (assessed daily by dentists, reported graphically as median score over 14 days, unable to use data) • Oral pain: 0 (no pain) to 100 (worst pain) VAS (assessed daily by participant, reported graphically as median score over 14 days, unable to use data) • Normalcy of diet: incidence of total parenteral nutrition (started when patients were unable to eat for longer than 3 days) • Number of days in hospital (reported as median, unable to use data) • Opioid analgesic use (reported as incidence; number of days of treatment with opioid analgesics is an outcome of this review and therefore we did not use these data) • Blood measurements (not an outcome of this review) • Fever (not an outcome of this review) • Infection (not an outcome of this review) • Antibiotic use (not an outcome of this review)
Notes	<p>Sample size calculation: not reported ("GM-CSF was supplied by the sponsor for 18 patients so that 36 patients could be included in the study. This should be enough to demonstrate a clinically significant difference")</p> <p>Funding: "We thank Novartis and Schering-Plough for supplying the GM-CSF" (pharmaceutical industry)</p> <p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: N/A</p> <p>Other information of note: GM-CSF administration only began after the conditioning treatment had been completed, by which point oral mucositis may have already begun to develop</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "the patients were randomized to receive GM-CSF or placebo" Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "the patients were randomized to receive GM-CSF or placebo" Comment: insufficient information to determine method of random sequence generation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-blind placebo-controlled" and "There was no difference in taste or appearance between the placebo and the GM-CSF" Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-blind placebo-controlled" and "There was no difference in taste or appearance between the placebo and the GM-CSF" Comment: it is not clear who was blinded. There are subjective elements to the assessment of lower grades of oral mucositis using the WHO scale, requiring the patient's assessment of pain/soreness and their ability to swallow. Higher grades have more objective elements so may not be affected by potential lack of blinding of the assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analyses
Selective reporting (reporting bias)	Low risk	Data for outcomes of this review were reported appropriately
Other bias	Low risk	No other sources of bias are apparent

Methods	<p>Trial design: parallel (4 arms)</p> <p>Location: South Korea</p> <p>Number of centres: 6</p> <p>Study duration: recruitment from January to August 2007</p> <p>Trials registry number: none/unknown</p>
Participants	<p>Inclusion criteria: 18 years or older with histological evidence of head and neck cancer; due to receive at least 5 weeks of primary RT, primary chemoradiotherapy, or postoperative RT; agreement to have complete medical history and physical examination; ECOG score of 0 to 2; white blood counts $3 \times 10^3/L$ or higher; platelet counts $100 \times 10^3/L$ or higher</p> <p>Exclusion criteria: oral ulcers; herpes simplex virus; severe periodontal disease; serum creatine levels greater than 2 mg/dL; ALT/AST values greater than 200 IU/L; cytotoxic chemotherapy or RT within 3 weeks of the start of the study; systemic or topical corticosteroids within 30 days of the start of the study; participated in another clinical study within 30 days of the start of the study</p> <p>Cancer type: head and neck: nasopharynx (Group A: 36%; Group B: 32%); oropharynx (Group A: 24%; Group B: 25%); oral cavity (Group A: 19%; Group B: 25%); hypopharynx (Group A: 2%; Group B: 4%); other (Group A: 19%; Group B: 14%)</p> <p>Cancer treatment:</p> <ul style="list-style-type: none"> • Radiotherapy: conventional fractionation once daily in 2 (± 0.25) Gy fractions, 5 times per week, for at least 5 weeks • Chemotherapy: concurrent cisplatin was allowed (just over 50% per group received this) <p>Age at baseline (years): Group A: median 56 (range 18 to 75); Group B: median 51 (range 18 to 77)</p> <p>Gender: Group A: 69% male; Group B: 57% male</p> <p>Number randomised: 113 (Group A: 85; Group B: 28)</p> <p>Number evaluated: 103 (Group A: 76; Group B: 27) for incidence of moderate to severe mucositis; 94 (Group A: 70; Group B: 24) for incidence of severe mucositis</p>
Interventions	<p>Comparison: EGF (recombinant human) versus placebo</p> <p>Group A: EGF</p> <ul style="list-style-type: none"> • (n = 29): 10 µg daily by oral spray, applied twice daily, sprayed over the entire oral mucosa and then swallowed, no oral intake for 30 minutes afterwards; starting on first day of RT and continuing for 5 weeks • (n = 29): 50 µg daily as above • (n = 27): 100 µg daily as above <p>Group B: placebo as above</p> <p>All participants gargled with chlorhexidine to maintain oral hygiene</p> <p>Compliance: not reported</p> <p>Duration of treatment: 5 weeks</p>
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: RTOG 0 to 4 scale (assessed weekly by radiation oncologists, reported as incidence of grade 2 to 4 and grade 3 to 4 at week 4 or 5; unclear reporting for grade 3 to 4, unable to use data) (time to develop mucositis also assessed but not an outcome of this review) • WHO oral toxicity grade (assessed weekly, not clear whether this is the WHO 0 to 4 scale for oral mucositis, no data reported)

	<ul style="list-style-type: none"> • Interruptions to cancer treatment (incidence of 3 or more consecutive days of interruption to RT) • Oral pain (assessed weekly, no description of scale used, no data reported) • Averse events (no data reported; narrative only) • Opioid analgesic use (assessed weekly, not clear if duration, quantity or incidence of use was assessed, no data reported) • Weight (not an outcome of this review) • Laboratory measurements (not an outcome of this review)
Notes	<p>Sample size calculation: allowing for 10% attrition, 26 participants per group required</p> <p>Funding: “This study was supported by a grant from the National R&D Program for Cancer Central, Ministry of Health, Welfare and Family Affairs, Republic of Korea (0620270)” (government) and “The EGF and placebo treatments were supplied free of charge” (presumably pharmaceutical industry)</p> <p>Declarations/conflicts of interest: not reported</p> <p>Data handling by review authors: we combined the 3 EGF groups to make a single pairwise comparison against placebo; no formal statistical analysis was undertaken for the different EGF dosages</p> <p>Other information of note: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “We assigned patients randomly to 4 arms” Comment: insufficient information to determine method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: “We assigned patients randomly to 4 arms” Comment: insufficient information to determine method of random sequence generation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “double-blind, placebo-controlled” and “Three concentrations of EGF and a placebo containing the drug delivery vehicle were manufactured, packaged, and supplied in a double-blind fashion” Comment: the use of a placebo should have ensured that blinding was successful
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “double-blind, placebo-controlled” Comment: it is not clear who was blinded. There are subjective elements to the assessment of most grades of oral mucositis using the RTOG scale, requiring the patient's as-

		assessment of pain. Grade 4 is more objective so may not be affected by potential lack of blinding of the assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition was 9% (Group A: 11%; Group B: 4%). Slight differential between groups but the reasons were reported and mostly unrelated to interventions/outcomes. Unlikely to have biased the results
Selective reporting (reporting bias)	High risk	Several outcomes were assessed but not properly reported ("No secondary endpoint showed any difference between the placebo and study groups")
Other bias	Low risk	No other sources of bias are apparent

5FU = fluorouracil; AJCC = American Joint Committee on Cancer; ALL = acute lymphoblastic leukaemia; allogeneic = cells from donor; AML = acute myelogenous leukaemia; AUC = area under the curve; autologous = patients' own cells; BMT = bone marrow transplantation; CALGB = Cancer and Leukaemia Group B; cGy = centigray; CML = chronic myelogenous leukaemia; CRT = chemoradiotherapy; CT = chemotherapy; ECOG = Eastern Co-operative Oncology Group; EGF = epidermal growth factor; EQ-5D = European Quality Of Life Utility Scale; FACT = Functional Assessment of Cancer Therapy; FDA = US Food and Drug Administration; G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; GVHD = graft-versus-host disease; Gy = gray; HLA = human leukocyte antigen; HSCT = haematopoietic stem cell transplantation; IA = intra-arterial; ITF = intestinal trefoil factor; ITT = intention-to-treat; IV = intravenous; KGF = keratinocyte growth factor; MDS = myelodysplastic syndrome; N/A = not applicable; NCI-CTC = National Cancer Institute common toxicity criteria; NHL = non-Hodgkin's lymphoma; NIH = National Institutes of Health; OMAS = oral mucositis assessment scale; OMDQ = oral mucositis daily questionnaire; OMWQ-HN = Oral Mucositis Weekly Questionnaire - Head and Neck cancer; PBPC = peripheral blood progenitor cell; PBSCT = peripheral blood stem cell transplantation; PEG = percutaneous endoscopic gastrostomy; PP = per protocol; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; SCC = squamous cell carcinoma; SCT = stem cell transplantation; SD = standard deviation; SMD = standardised mean difference; TBI = total-body irradiation; TGF = transforming growth factor; TPN = total parenteral nutrition; VAS = visual analogue scale; WBC = white blood cell; WHO = World Health Organization; WCCNR = Western Consortium for Cancer Nursing Research.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Antin 2002	Recombinant human interleukin-11 versus placebo. Study stopped early due to adverse event triggering preset stopping rule - data only for 10 patients in rhIL group and 3 placebo
de Koning 2007	TGF-beta(2) versus placebo. Cross-over study with no first period data reported (see Types of studies)
Foncuberta 2001	TGF-beta(3) versus placebo. Participants assigned sequentially, not randomised

(Continued)

Gebbia 1994	G-CSF versus thymopentin versus G-CSF plus thymopentin versus placebo. Oral mucositis not mentioned (unknown if measured)
Gladkov 2013	G-CSF (lipegfilgrastim) versus G-CSF (pegfilgrastim). Oral mucositis not mentioned (unknown if measured). Insufficient information (abstract)
Gordon 1993	GM-CSF versus no treatment. Unclear if randomised or not. Only 13 participants. Insufficient information (abstract)
Horsley 2007	KGF (palifermin) versus standard care. No random allocation
Hunter 2009	ATL-104 versus placebo. Not RCT - this study combines patients who were in cohorts with increasing doses of mouthrinse to assess safety, with an RCT
Ifrah 1999	GM-CSF versus placebo. Primary outcome was survival/cure, with mucositis as a toxicity. Unclear if mucositis was oral or gastrointestinal
Iwase 1997	G-CSF versus no treatment. No mention of randomisation and no description of when intervention given in relation to cancer treatment
Jones 1996	GM-CSF versus placebo. Unclear if mucositis was oral or gastrointestinal
Karthus 1998	G-CSF versus placebo. Only 8 patients, 32 chemotherapy cycles and results presented assuming independent
Kubo 2016	G-CSF (pegfilgrastim) versus G-CSF (filgrastim). Incidence of stomatitis reported in adverse events table Trials registry number: JapicCTI-111394
Lee 2016	G-CSF (pegteograstim) versus G-CSF (pegfilgrastim). Incidence of stomatitis reported in adverse events table Trials registry number: NCT01328938
Legros 1997	GM-CSF versus placebo. Unclear if mucositis was oral or gastrointestinal
Limaye 2013	AG013 versus placebo. AG013 is composed of recombinant <i>Lactococcus lactis</i> engineered to secrete human Trefoil Factor 1. Randomised at first but participants not developing oral mucositis in chemotherapy cycle 1 were excluded from the next phase where oral mucositis was measured, so randomisation was lost Trials registry number: NCT00938080
Nabholtz 2002	G-CSF (leridistim) versus G-CSF (filgrastim). Incidence of stomatitis reported in adverse events table
NCT00360971	KGF (palifermin) versus placebo. Study terminated at 21 participants (298 planned) due to positive preliminary results from other palifermin studies
NCT00626639	KGF (palifermin) versus placebo. Study terminated at 5 participants due to departure of principal investigator and slow enrolment
Pettengell 1992	G-CSF versus no treatment. Unclear if mucositis was oral or gastrointestinal

(Continued)

Ryu 2007	GM-CSF versus placebo. Some participants (6%) had oral mucositis at baseline Trials registry number: NCT00008398
Throuvalas 1995	GM-CSF versus no treatment. Probably not RCT - described as comparative study. Only 10 participants. Insufficient information (abstract)
Tsurusawa 2016	G-CSF versus no treatment. Incidence of stomatitis reported in adverse events table Trials registry number: UMIN ID: 000000675
Vitale 2014	KGF (palifermin) versus no treatment. From full text it is not RCT - retrospective and allocation of KGF/no KGF based on doctor's decision

G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; KGF = keratinocyte growth factor; RCT = randomised controlled trial; rhIL = recombinant human interleukin; TGF = transforming growth factor.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[ACTRN12606000083594](#)

Methods	Multicentre, double-blind, randomised placebo-controlled trial
Participants	18 years or older with lymphoma and due to undergo high-dose BEAM chemotherapy and autologous stem cell transplantation as inpatient
Interventions	Whey growth factor extract at 13.5 mg/mL in sterile saline versus placebo (sterile saline)
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale • Normalcy of diet: incidence of enteral/parenteral feeding • Duration of opiate analgesics • Quality of life: OMDQ • Adverse events
Notes	Funding: commercial sector/industry (TGR Biosciences, Australia) Contact: correspondence with pharmaceutical company suggests no benefit

[Antonadou 1998](#)

Methods	Multicentre, randomised controlled trial (no placebo)
Participants	Head and neck cancer; receiving continuous course of radiotherapy for 6 to 7 weeks
Interventions	GM-CSF (subcutaneous) versus no treatment
Outcomes	Signs and symptoms of oral mucositis: erythema, pain and dysphagia each measured on 0 to 3 scale

Antonadou 1998 (Continued)

Notes	Abstract only (we were unable to link this abstract to a full-text report) Some P values suggest benefit for GM-CSF at some time points Quote: “GM-CSF reduces the incidence and severity of radiation mucositis and allows the completion of the XRT treatment without protraction”
-------	--

Elsaid 2001

Methods	Randomised controlled trial (no placebo)
Participants	Anaemic participants with head and neck cancer receiving radiotherapy once daily (1.8 Gy or 2 Gy) to doses of 66 Gy to 70 Gy
Interventions	Recombinant human erythropoietin versus no treatment
Outcomes	Incidence of grade 3 mucositis and dermatitis
Notes	Abstract only (we were unable to link this abstract to a full-text report) Higher rate of mucositis in the no-treatment group (5.9% versus 0%)

Grzegorzczak 2006

Methods	Randomised placebo-controlled trial
Participants	Adults (aged 19 to 68 years) undergoing haematopoietic stem cell transplantation
Interventions	G-CSF versus placebo
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale • Oral pain: 0 to 10 VAS • Neutrophil counts
Notes	Translation provided insufficient information. Discrepancy between graph legends and descriptions Unable to contact author

Koga 2015

Methods	Randomised controlled trial (no placebo)
Participants	Children with B-cell non-Hodgkin's lymphoma (B-NHL) receiving chemotherapy
Interventions	G-CSF versus no treatment
Outcomes	<ul style="list-style-type: none"> • Oral mucositis (no further details) • Duration of hospitalisation • Incidence of febrile neutropenia • Infections

Koga 2015 (Continued)

	<ul style="list-style-type: none"> • Time to neutrophil recovery • Costs
Notes	<p>Abstract only (we were unable to link this abstract to a full-text report)</p> <p>Quote: “G-CSF+ patients showed a positive impact on the meantime to neutrophil recovery and hospital stay, but they had no impact in incidences of febrile neutropenia, infections, stomatitis, and total cost”</p>

NCT00293462

Methods	Double-blind, randomised placebo-controlled trial (1 of the 3 arms is a cross-over)
Participants	18 years or older with head and neck cancer due to receive conventional or hyperfractionated radiotherapy or intensity-modulated radiotherapy (IMRT) with or without concurrent chemotherapy
Interventions	GM-CSF mouthwash versus salt and soda mouthwash versus both (cross-over arm)
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: scale/s unclear • Quality of life: 0 to 10 scale • Oral pain: 0 to 10 scale • Functional status by Karnofsky performance status scale
Notes	<p>Trials registry number: NCT00293462</p> <p>Funding: University of California, San Francisco; National Cancer Institute (NCI)</p>

NCT00393822

Methods	Double-blind, randomised placebo-controlled trial
Participants	18 years or older with resected colon cancer (American Joint Committee on Cancer Stage 2B or 3) and due to receive 5-FU and leucovorin
Interventions	KGF versus placebo
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale - incidence and duration of moderate to severe (grade 2 to 4) • Interruptions to cancer treatment • Mouth and throat pain • Adverse events • Survival • Changes in laboratory values • Serum anti-KGF antibody formation
Notes	<p>Trials registry number: NCT00393822</p> <p>Funding: Amgen (pharmaceutical industry)</p>

NCT02303197

Methods	Randomised controlled trial (no placebo)
Participants	Adults (aged 18 to 75 years) with head and neck cancer due to receive radiotherapy
Interventions	Recombinant human EGF versus Chining
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: RTOG 0 to 4 scale • Oral pain: VAS • Quality of life: EORTC QLQ-H&N35 • Weight change • Safety (blood/urine/kidney/liver/electrocardiogram)
Notes	Trials registry number: NCT02303197 Funding: Tianjin Medical University Cancer Institute and Hospital

NCT02313792

Methods	Double-blind, randomised placebo-controlled trial
Participants	16 years or older due to receive preparative cancer treatment regimen followed by autologous or allogeneic HSCT (cancer type not reported)
Interventions	KGF versus placebo
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: incidence and duration of severe (scale not reported) • Oral pain: VAS • Use of opioid analgesics • Quality of life (scale not reported) • Cost-effectiveness
Notes	Trials registry number: NCT02313792 Funding: The Catholic University of Korea; Collaborator: "BLNH" (probably pharmaceutical industry)

Patte 2002

Methods	Randomised controlled trial (no placebo)
Participants	Children with non-Hodgkin's lymphoma due to receive 2 courses of COPAD induction chemotherapy
Interventions	G-CSF versus no treatment
Outcomes	<ul style="list-style-type: none"> • Mucositis (unclear if oral or gastrointestinal): 0 to 4 scale - incidence of severe (grade 3 to 4) • Duration of hospitalisation • Febrile neutropenia • Severe infections • Blood measurements • Use of IV antifungals or antibiotics • Survival

Patte 2002 (Continued)

Notes	Quote: "The incidence of grade 3 and 4 mucositis was similar in both arms" Contact: emailed corresponding author July 2017 to clarify if mucositis is oral or gastrointestinal
-------	---

Schuster 2007a

Methods	Multicentre, double-blind, randomised placebo-controlled trial
Participants	18 years or older with multiple myeloma or lymphoma due to receive high-dose chemotherapy (with or without TBI) followed by autologous HSCT
Interventions	Recombinant human FGF-20 (velafermin) (3 arms with different dosages) versus placebo
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale - incidence and duration of severe (grade 3 to 4) • Adverse events
Notes	Abstract only (we were unable to link this abstract to a full-text report) Trials registry number: NCT00104065

Schuster 2007b

Methods	Multicentre, double-blind, randomised placebo-controlled trial
Participants	18 years or older with multiple myeloma or lymphoma undergoing high-dose chemotherapy (with or without TBI) followed by autologous HSCT
Interventions	Recombinant human FGF-20 (velafermin) (3 arms with different dosages) versus placebo
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale - incidence of severe (grade 3 to 4) • Adverse events
Notes	Abstract only (we were unable to link this abstract to a full-text report) Trials registry number: NCT00323518

Shea 2007

Methods	Randomised controlled trial (no placebo)
Participants	Aged 18 to 74 years with lymphoma, leukaemia or multiple myeloma; TBI plus high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation
Interventions	KGF (4 arms with different schedules)
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale • Mouth and throat pain: OMDQ • Opioid analgesic use • Adverse events

Shea 2007 (Continued)

Notes	Abstract only (we were unable to link this abstract to a full-text report) Trials registry number: NCT00109031
-------	---

Spielberger 2001

Methods	Multicentre, double-blind, randomised placebo-controlled trial
Participants	Haematologic malignancies; eligible for TBI plus high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation; aged 12 to 65 years
Interventions	KGF (7 doses) versus KGF (4 doses + 3 doses of placebo) versus placebo (7 doses)
Outcomes	<ul style="list-style-type: none"> • Oral mucositis: WHO 0 to 4 scale - incidence and duration of severe (grade 3 to 4) • Use of opioid analgesics • Quality of life • Febrile neutropenia • Use of IV antifungals or antibiotics • Diarrhoea
Notes	Abstract only (we were unable to link this abstract to a full-text report) Trials registry number: NCT00004132

5FU = fluorouracil; EGF = epidermal growth factor; EORTC QLQ-H&N35 = European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire, Head and Neck Module; G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; HSCT = haematopoietic stem cell transplantation; IV = intravenous; KGF = keratinocyte growth factor; NCI-CTC = National Cancer Institute common toxicity criteria; OMDQ = oral mucositis daily questionnaire; FGF-20 = fibroblast growth factor-20; TBI = total-body irradiation; VAS = visual analogue scale; WHO = World Health Organization.

DATA AND ANALYSES

Comparison 1. KGF versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 BMT/SCT after conditioning for haematological cancers	4	655	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.88, 1.05]
1.2 RT to head & neck with cisplatin	2	374	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.90, 1.00]
1.3 CT alone for mixed cancers	2	215	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.60, 0.85]
2 Oral mucositis (moderate + severe)	13		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 BMT/SCT after conditioning for haematological cancers	6	852	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 0.99]
2.2 RT to head & neck with cisplatin/5FU	3	471	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.83, 1.00]
2.3 CT alone for mixed cancers	4	344	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.45, 0.70]
3 Oral mucositis (severe)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 BMT/SCT after conditioning for haematological cancers	6	852	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.11]
3.2 RT to head & neck with cisplatin/5FU	3	471	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.69, 0.90]
3.3 CT alone for mixed cancers	3	263	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.14, 0.65]
4 Interruptions to cancer treatment (unscheduled RT breaks of 5 or more days)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 RT to head & neck with cisplatin/5FU	3	473	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.65, 1.59]
5 Interruptions to cancer treatment (chemotherapy delays/discontinuations)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 RT to head & neck with cisplatin	2	374	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.62, 1.47]
6 Oral pain	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 BMT/SCT after conditioning for haematological cancers	1	42	Mean Difference (IV, Random, 95% CI)	-0.85 [-3.00, 1.30]
6.2 RT to head & neck with cisplatin	2	374	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.27, 0.02]

7 Normalcy of diet (use of supplemental nutrition)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 BMT/SCT after conditioning for haematological cancers	4	714	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.58, 1.34]
7.2 RT to head & neck with cisplatin/5FU	3	473	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.77, 1.37]
8 Normalcy of diet (worst ability to eat score - 1 to 4 scale)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 BMT/SCT after conditioning for haematological cancers	1	42	Mean Difference (IV, Random, 95% CI)	-0.5 [-1.21, 0.21]
9 Number of days in hospital	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 BMT/SCT after conditioning for haematological cancers	1	281	Mean Difference (IV, Random, 95% CI)	0.0 [-1.64, 1.64]
10 Number of days of treatment with opioid analgesics	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 BMT/SCT after conditioning for haematological cancers	2	323	Mean Difference (IV, Random, 95% CI)	-1.41 [-3.33, 0.51]

Comparison 2. KGF (dose comparison)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 BMT/SCT after conditioning for haematological cancers	1	224	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.75, 1.03]
2 Oral mucositis (moderate + severe)	3		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 BMT/SCT after conditioning for haematological cancers	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 CT alone for metastatic colorectal cancer	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Oral mucositis (severe)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 BMT/SCT after conditioning for haematological cancers	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Oral pain (maximum score on 0 to 10 VAS)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 BMT/SCT after conditioning for haematological cancers	1	28	Mean Difference (IV, Random, 95% CI)	0.70 [-1.90, 3.30]
5 Normalcy of diet (use of TPN)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

5.1 BMT/SCT after conditioning for haematological cancers	1	224	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.63, 1.02]
6 Normalcy of diet (worst ability to eat score - 1 to 4 scale)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 BMT/SCT after conditioning for haematological cancers	1	28	Mean Difference (IV, Random, 95% CI)	0.40 [-0.41, 1.21]
7 Number of days in hospital	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 BMT/SCT after conditioning for haematological cancers	1	224	Mean Difference (IV, Random, 95% CI)	0.0 [-1.78, 1.78]
8 Number of days of treatment with opioid analgesics	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 BMT/SCT after conditioning for haematological cancers	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. KGF versus chlorhexidine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CT alone for haematological cancer	1	90	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.54, 0.85]
2 Oral mucositis (moderate + severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CT alone for haematological cancer	1	90	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.05, 0.28]
3 Oral mucositis (severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 CT alone for haematological cancer	1	90	Risk Ratio (M-H, Random, 95% CI)	0.01 [0.00, 0.19]

Comparison 4. GM-CSF versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 BMT/SCT after conditioning for mixed cancers	1	90	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.04]
1.2 RT to head & neck	1	29	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.82, 1.23]
2 Oral mucositis (moderate + severe)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

2.1 BMT/SCT after conditioning for haematological cancers	1	109	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.13]
2.2 RT to head & neck	1	29	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.06]
3 Oral mucositis (severe)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 BMT/SCT after conditioning for mixed cancers	3	235	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.33, 1.67]
3.2 RT to head & neck	1	29	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.09]
3.3 CT alone for mixed cancers	2	65	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.05, 7.11]
4 Oral pain (maximum score on 0 to 10 VAS)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 BMT/SCT after conditioning for mixed cancers	1	90	Mean Difference (IV, Random, 95% CI)	0.60 [-0.85, 2.05]
5 Normalcy of diet (use of feeding tube/parenteral nutrition)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 BMT/SCT after conditioning for haematological cancers	1	36	Risk Ratio (M-H, Random, 95% CI)	1.1 [0.63, 1.91]
5.2 RT to head & neck	1	29	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.09]
6 Number of days of treatment with opioid analgesics	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 BMT/SCT after conditioning for mixed cancers	1	90	Mean Difference (IV, Random, 95% CI)	-1.10 [-1.91, -0.29]

Comparison 5. GM-CSF (dose comparison)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CT alone for breast cancer	1	36	Risk Ratio (M-H, Random, 95% CI)	2.75 [1.07, 7.04]

Comparison 6. GM-CSF versus sucralfate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (moderate + severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 RT to head & neck	1	40	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.80, 1.14]
2 Oral mucositis (severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 RT to head & neck	1	40	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.24, 1.21]
3 Interruptions to cancer treatment	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 RT to head & neck	1	40	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.36]
4 Normalcy of diet (use of PEG tube)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

4.1 RT to head & neck	1	40	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.01, 3.56]
-----------------------	---	----	----------------------------------	-------------------

Comparison 7. G-CSF versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 RT to head & neck	2	54	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.86, 1.22]
1.2 CT alone for lung cancer	1	195	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.40, 0.87]
2 Oral mucositis (moderate + severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CT alone for breast cancer	1	14	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.12, 0.95]
3 Oral mucositis (severe)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 RT to head & neck	2	54	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.15, 0.87]
4 Interruptions to cancer treatment (RT interruption)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 RT to head & neck	1	40	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.01, 4.31]
5 Normalcy of diet (use of PEG tube)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 RT to head & neck	1	40	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.01, 2.86]

Comparison 8. G-CSF (pegfilgrastim) versus G-CSF (filgrastim)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 BMT/SCT after conditioning for mixed cancers	1	61	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.27]
2 Oral mucositis (moderate + severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 BMT/SCT after conditioning for mixed cancers	1	61	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.11]
3 Normalcy of diet (use of supplemental nutrition)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 BMT/SCT after conditioning for mixed cancers	1	61	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.94, 1.06]

Comparison 9. EGF versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (moderate + severe)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 BMT/SCT after conditioning for haematological cancers	1	136	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.78, 1.43]
1.2 RT to head & neck +/- cisplatin	1	103	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.99]
2 Oral mucositis (severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 BMT/SCT after conditioning for haematological cancers	1	136	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.59, 1.80]
3 Interruptions to cancer treatment (RT breaks > 2 consecutive days)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 RT to head & neck +/- cisplatin	1	113	Risk Ratio (M-H, Random, 95% CI)	4.38 [0.25, 75.44]
4 Normalcy of diet (use of supplemental nutrition)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 BMT/SCT after conditioning for haematological cancers	1	136	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.55, 1.94]

Comparison 10. ITF versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CT alone for colorectal cancer	1	99	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.35, 0.79]
2 Oral mucositis (moderate + severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CT alone for colorectal cancer	1	99	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.10, 0.48]
3 Oral mucositis (severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 CT alone for colorectal cancer	1	99	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.06, 36.39]

Comparison 11. ITF (dose comparison)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CT alone for colorectal cancer	1	66	Risk Ratio (M-H, Random, 95% CI)	1.3 [0.67, 2.54]
2 Oral mucositis (moderate + severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CT alone for colorectal cancer	1	66	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.18, 3.09]
3 Oral mucositis (severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 CT alone for colorectal cancer	1	66	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.90]

Comparison 12. Erythropoietin versus placebo

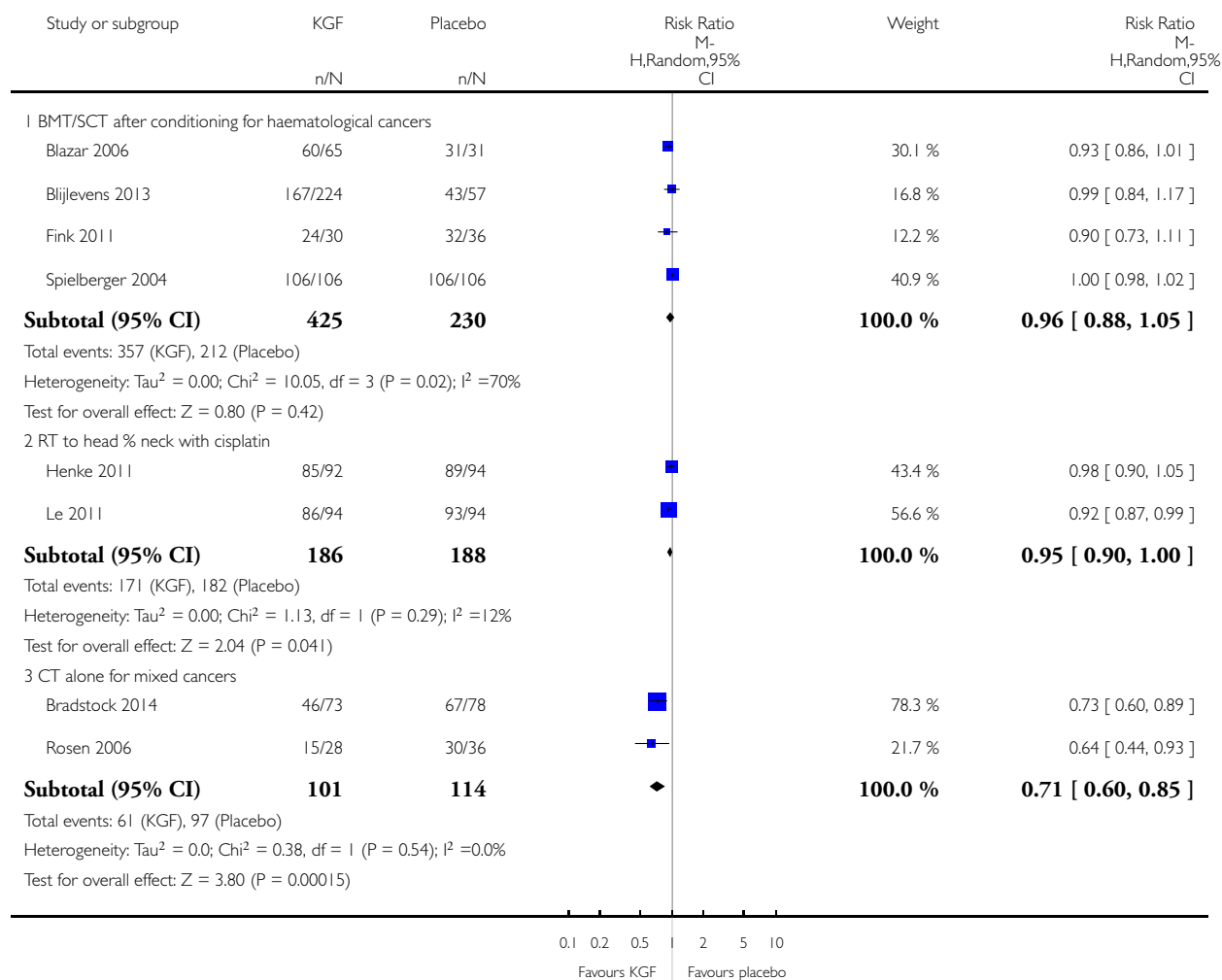
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral mucositis (any)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 BMT/SCT after conditioning for haematological cancers	1	80	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.21, 0.60]
2 Oral mucositis (moderate + severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 BMT/SCT after conditioning for haematological cancers	1	80	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.24, 0.79]
3 Oral mucositis (severe)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 BMT/SCT after conditioning for haematological cancers	1	80	Risk Ratio (M-H, Random, 95% CI)	0.4 [0.14, 1.17]
4 Number of days in hospital	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 BMT/SCT after conditioning for haematological cancers	1	80	Mean Difference (IV, Random, 95% CI)	-2.95 [-7.73, 1.83]

Analysis 1.1. Comparison 1 KGF versus placebo, Outcome 1 Oral mucositis (any).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 1 Oral mucositis (any)

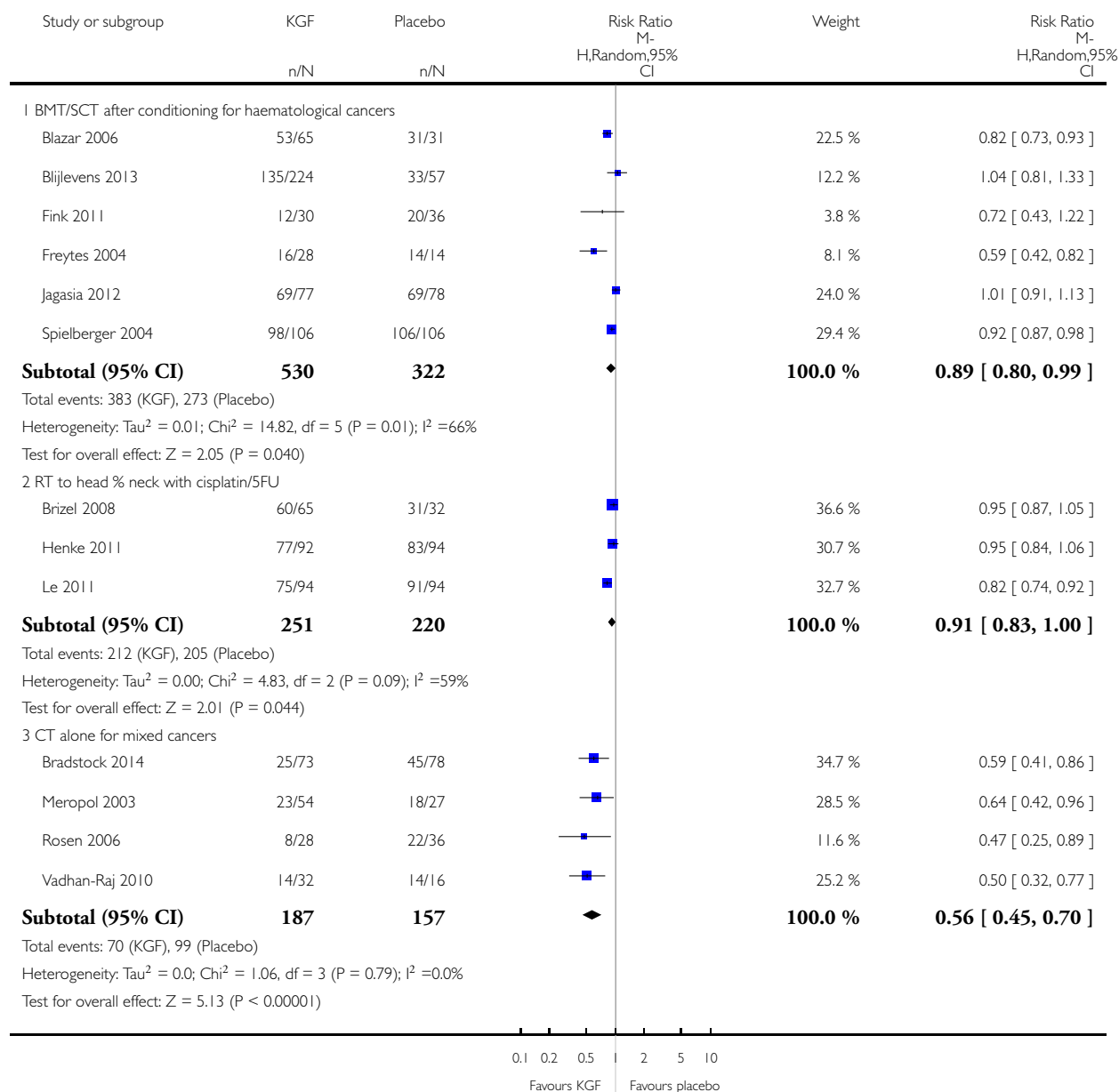


Analysis 1.2. Comparison 1 KGF versus placebo, Outcome 2 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 2 Oral mucositis (moderate + severe)

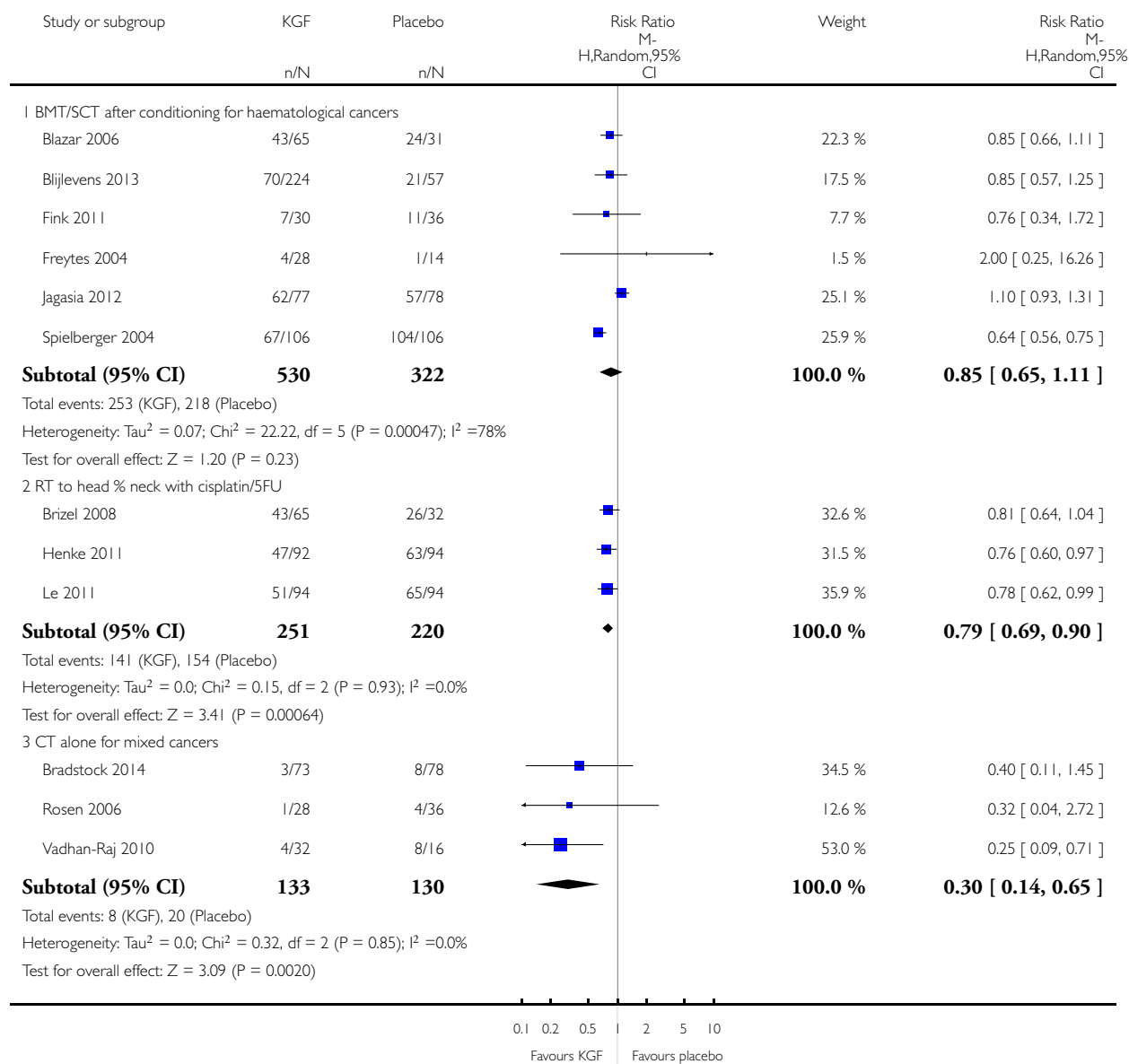


Analysis 1.3. Comparison 1 KGF versus placebo, Outcome 3 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 3 Oral mucositis (severe)

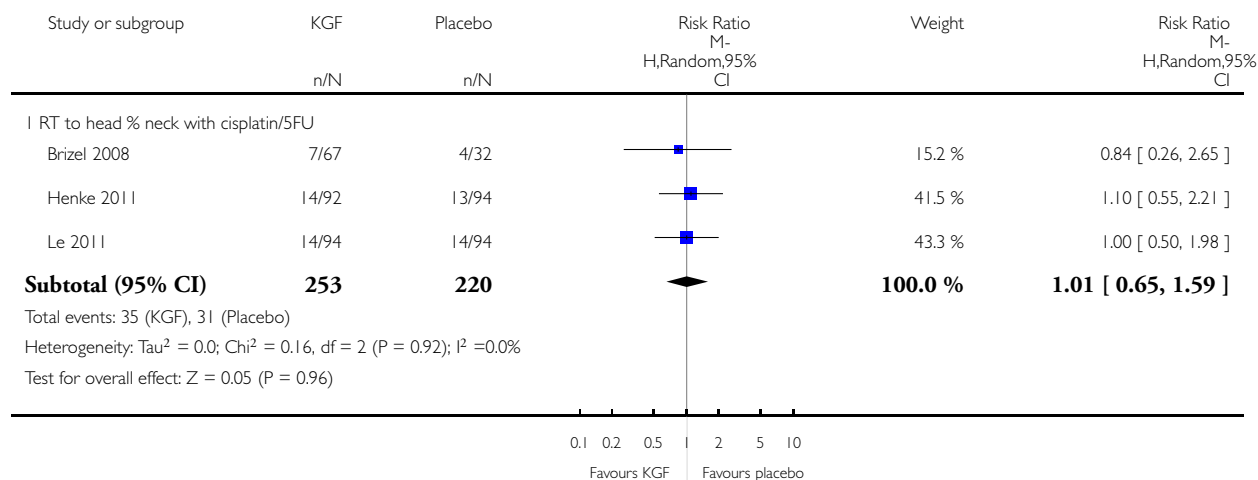


Analysis 1.4. Comparison 1 KGF versus placebo, Outcome 4 Interruptions to cancer treatment (unscheduled RT breaks of 5 or more days).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 4 Interruptions to cancer treatment (unscheduled RT breaks of 5 or more days)

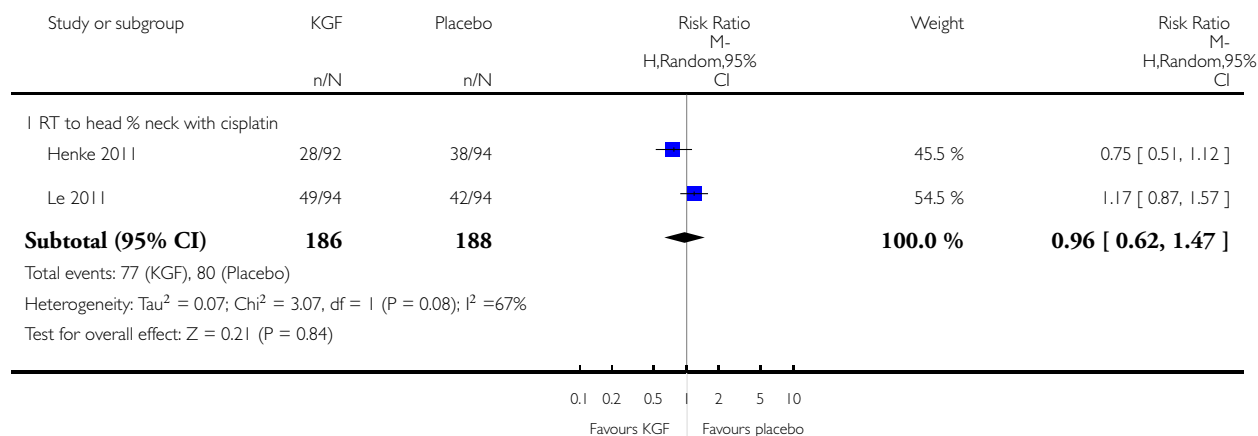


Analysis 1.5. Comparison 1 KGF versus placebo, Outcome 5 Interruptions to cancer treatment (chemotherapy delays/discontinuations).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 5 Interruptions to cancer treatment (chemotherapy delays/discontinuations)

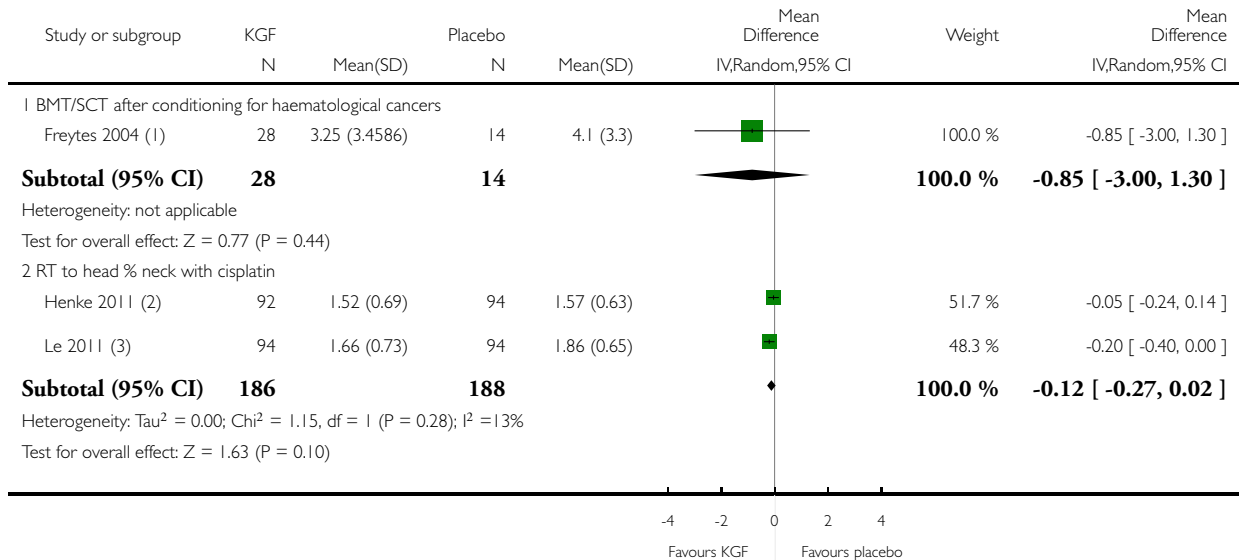


Analysis 1.6. Comparison 1 KGF versus placebo, Outcome 6 Oral pain.

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 6 Oral pain



(1) 0 (no pain) to 10 (worst pain) scale reporting mean worst score experienced

(2) 0 (no pain) to 4 (worst pain) reporting overall mean

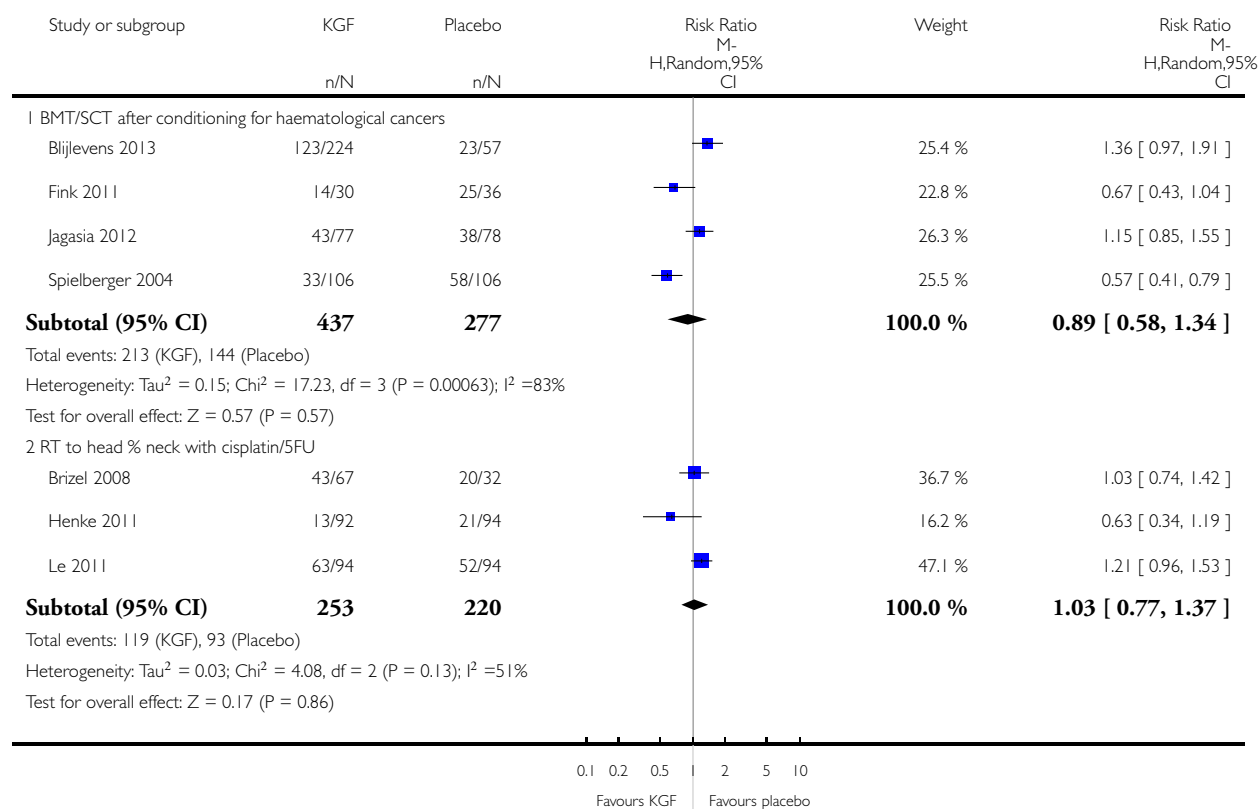
(3) 0 (no pain) to 4 (worst pain) reporting overall mean

Analysis 1.7. Comparison 1 KGF versus placebo, Outcome 7 Normalcy of diet (use of supplemental nutrition).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 7 Normalcy of diet (use of supplemental nutrition)

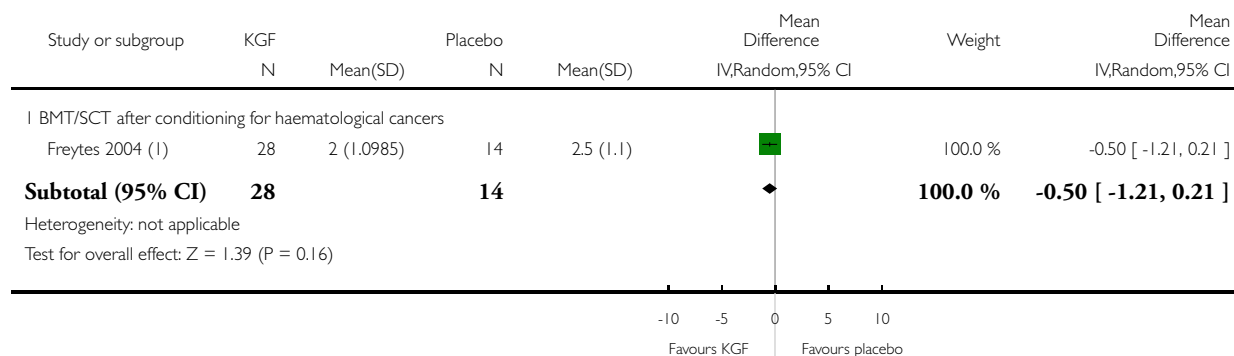


Analysis 1.8. Comparison 1 KGF versus placebo, Outcome 8 Normalcy of diet (worst ability to eat score - 1 to 4 scale).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 8 Normalcy of diet (worst ability to eat score - 1 to 4 scale)



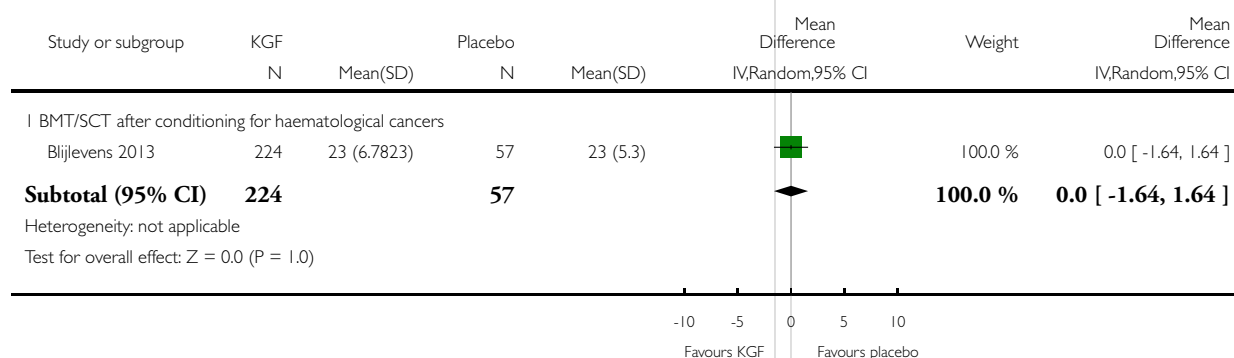
(1) Scale: 1 = normal, 2 = only soft solids, 3 = only liquids, 4 = no solids or liquids

Analysis 1.9. Comparison 1 KGF versus placebo, Outcome 9 Number of days in hospital.

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 9 Number of days in hospital

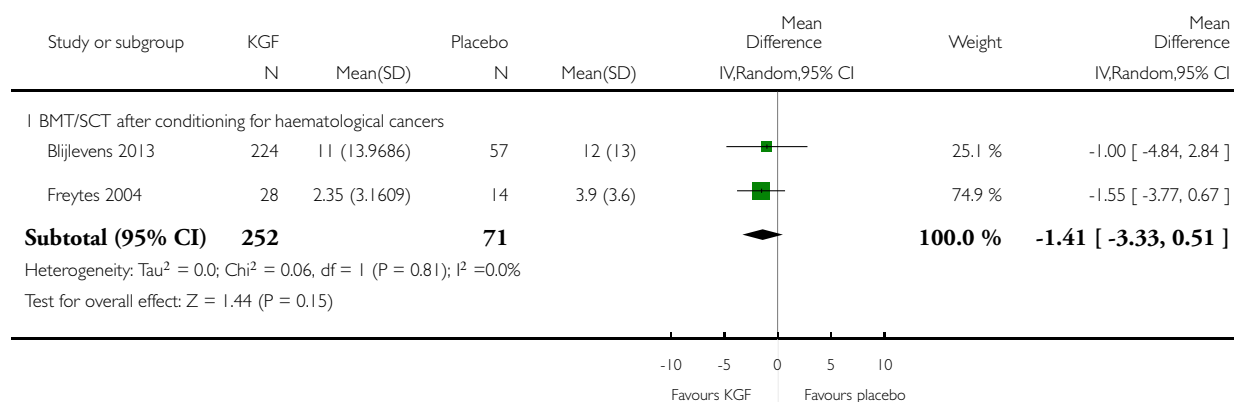


Analysis 1.10. Comparison 1 KGF versus placebo, Outcome 10 Number of days of treatment with opioid analgesics.

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 1 KGF versus placebo

Outcome: 10 Number of days of treatment with opioid analgesics

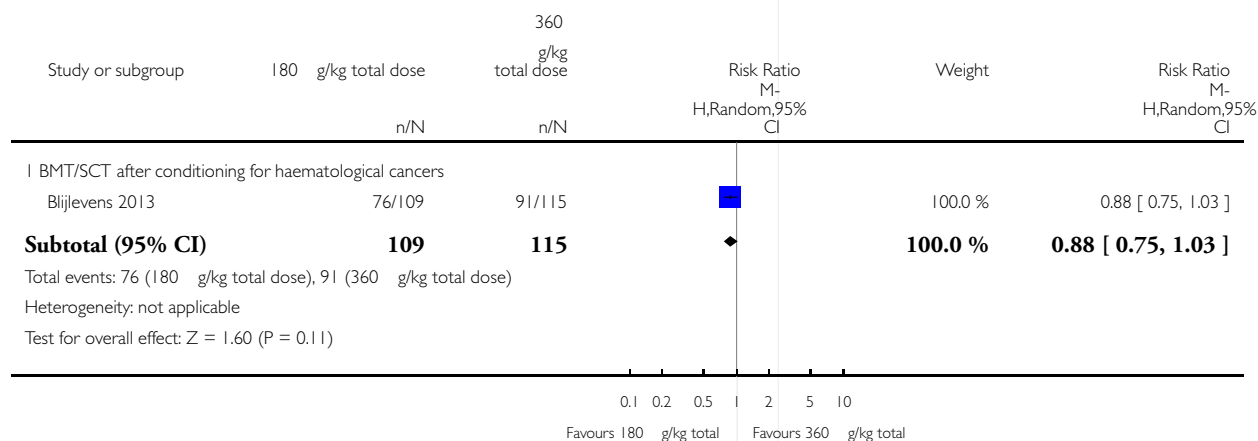


Analysis 2.1. Comparison 2 KGF (dose comparison), Outcome 1 Oral mucositis (any).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 2 KGF (dose comparison)

Outcome: 1 Oral mucositis (any)

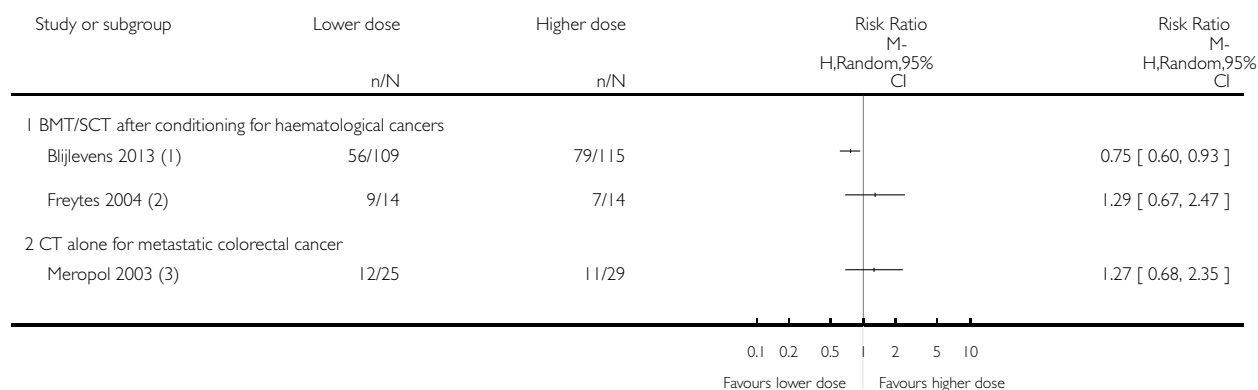


Analysis 2.2. Comparison 2 KGF (dose comparison), Outcome 2 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 2 KGF (dose comparison)

Outcome: 2 Oral mucositis (moderate + severe)



(1) Total dose: 180 vs 360 g/kg

(2) Total dose: 325 vs 650 g/kg

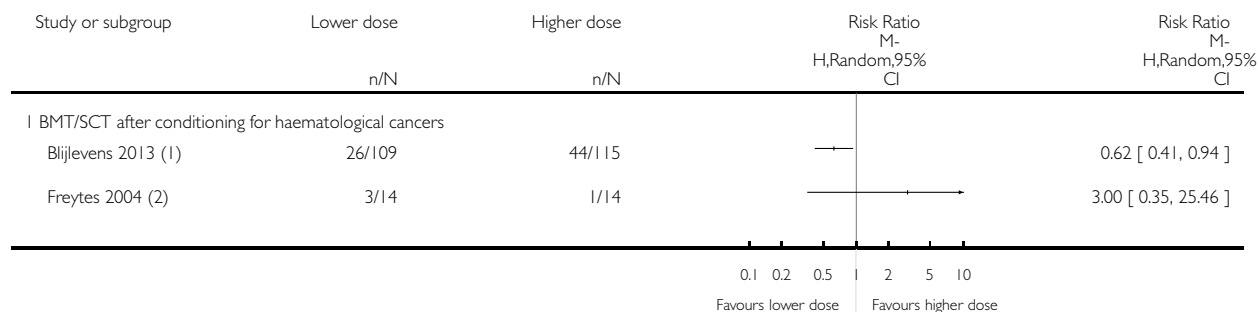
(3) Total dose: 3 to 60 vs 120 to 240 g/kg

Analysis 2.3. Comparison 2 KGF (dose comparison), Outcome 3 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 2 KGF (dose comparison)

Outcome: 3 Oral mucositis (severe)



(1) Total dose: 180 vs 360 g/kg

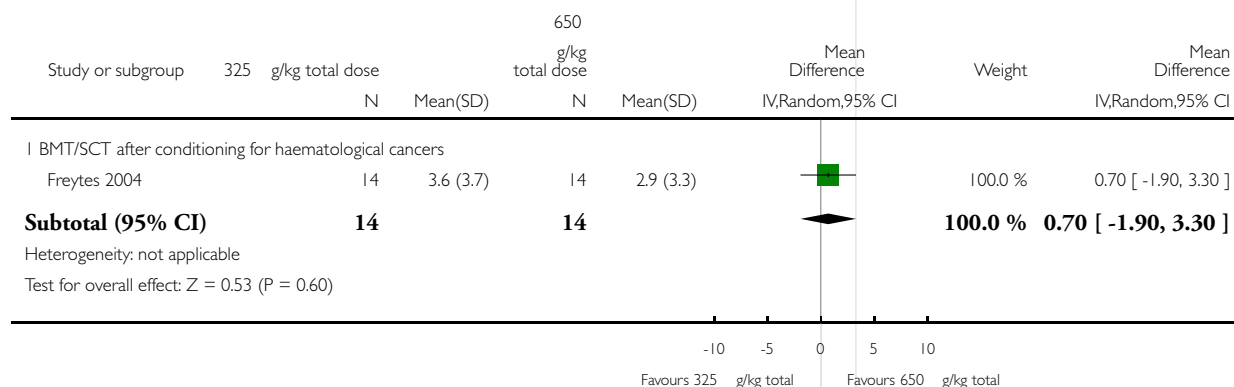
(2) Total dose: 325 vs 650 g/kg

Analysis 2.4. Comparison 2 KGF (dose comparison), Outcome 4 Oral pain (maximum score on 0 to 10 VAS).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 2 KGF (dose comparison)

Outcome: 4 Oral pain (maximum score on 0 to 10 VAS)

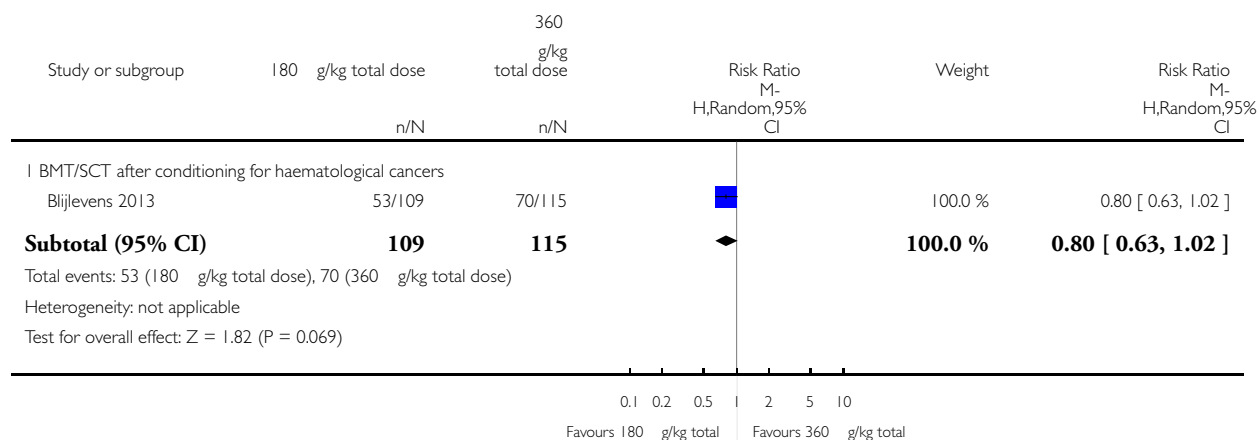


Analysis 2.5. Comparison 2 KGF (dose comparison), Outcome 5 Normalcy of diet (use of TPN).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 2 KGF (dose comparison)

Outcome: 5 Normalcy of diet (use of TPN)

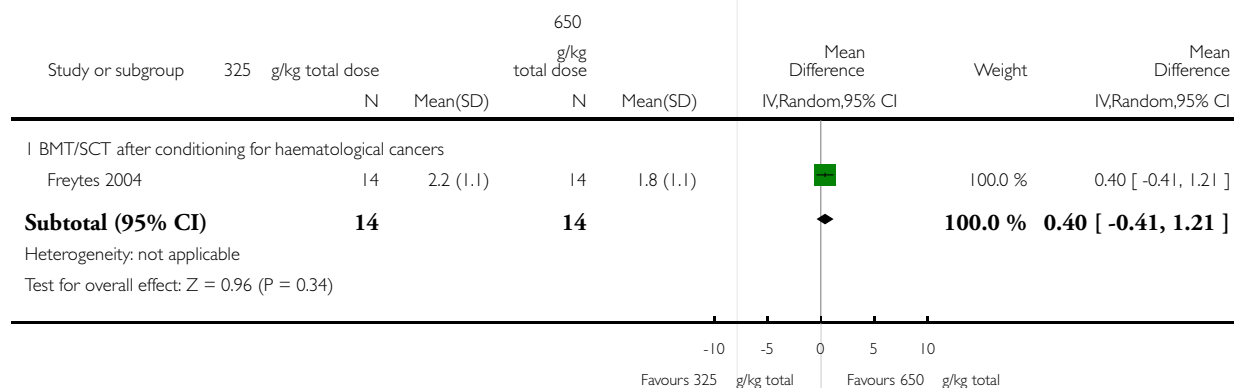


Analysis 2.6. Comparison 2 KGF (dose comparison), Outcome 6 Normalcy of diet (worst ability to eat score - 1 to 4 scale).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 2 KGF (dose comparison)

Outcome: 6 Normalcy of diet (worst ability to eat score - 1 to 4 scale)

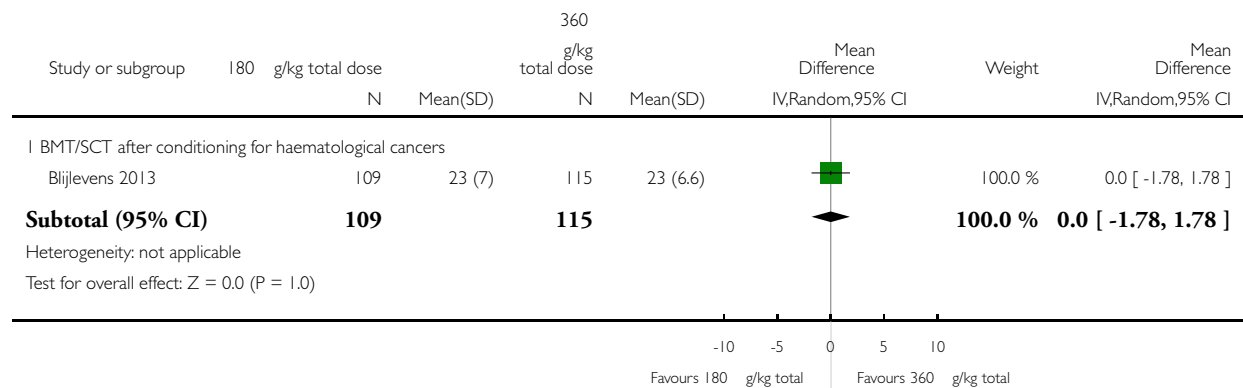


Analysis 2.7. Comparison 2 KGF (dose comparison), Outcome 7 Number of days in hospital.

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 2 KGF (dose comparison)

Outcome: 7 Number of days in hospital

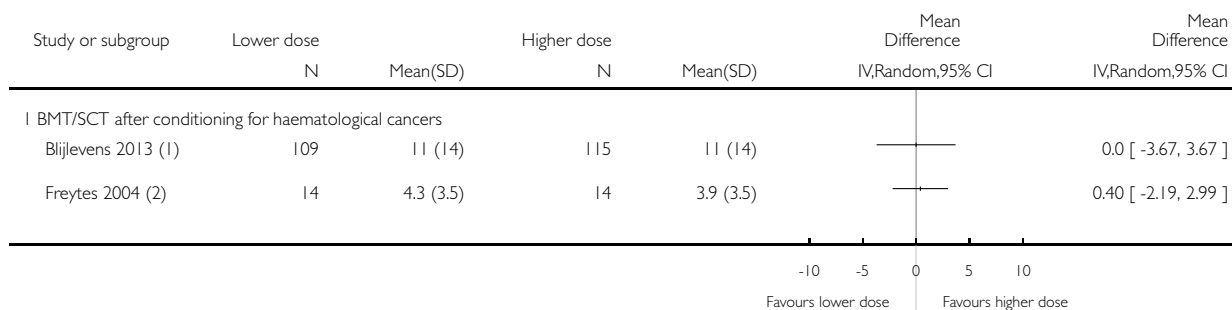


Analysis 2.8. Comparison 2 KGF (dose comparison), Outcome 8 Number of days of treatment with opioid analgesics.

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 2 KGF (dose comparison)

Outcome: 8 Number of days of treatment with opioid analgesics



(1) Total dose: 180 vs 360 g/kg

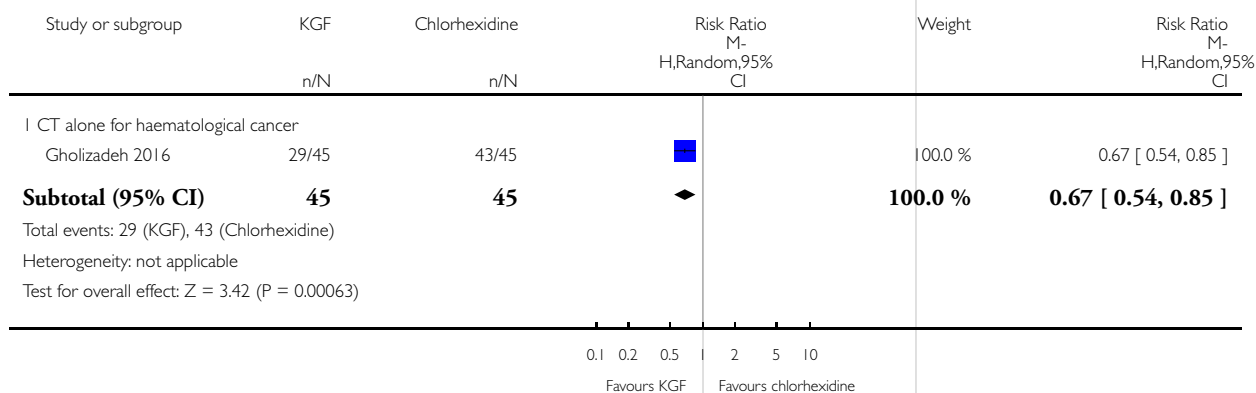
(2) Total dose: 325 vs 650 g/kg

Analysis 3.1. Comparison 3 KGF versus chlorhexidine, Outcome 1 Oral mucositis (any).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 3 KGF versus chlorhexidine

Outcome: 1 Oral mucositis (any)

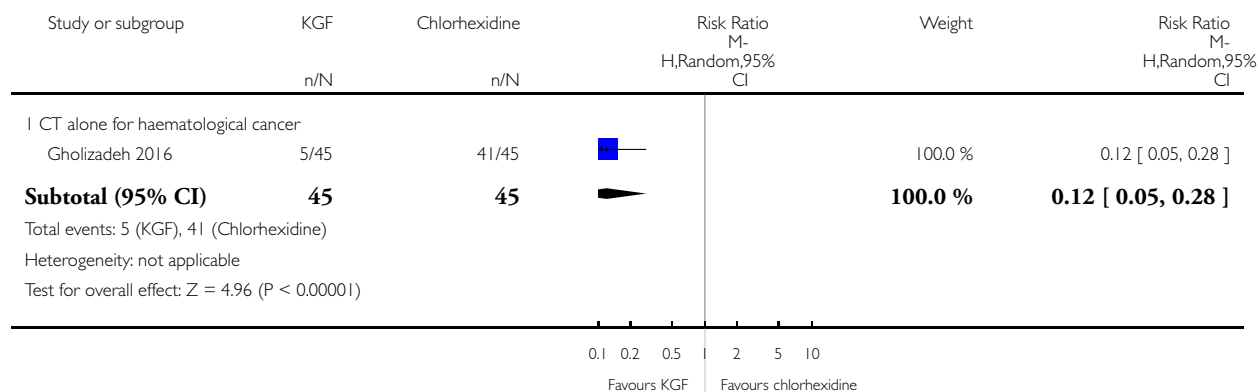


Analysis 3.2. Comparison 3 KGF versus chlorhexidine, Outcome 2 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 3 KGF versus chlorhexidine

Outcome: 2 Oral mucositis (moderate + severe)

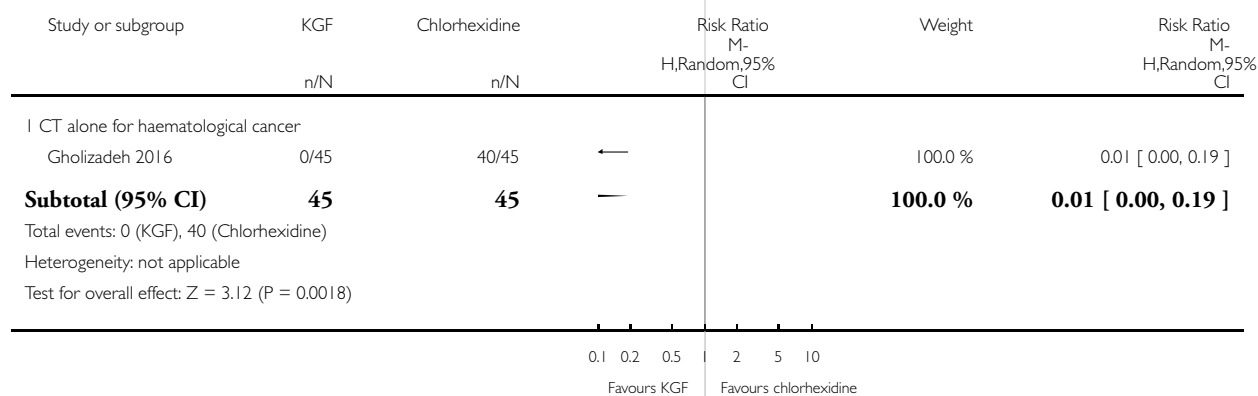


Analysis 3.3. Comparison 3 KGF versus chlorhexidine, Outcome 3 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 3 KGF versus chlorhexidine

Outcome: 3 Oral mucositis (severe)

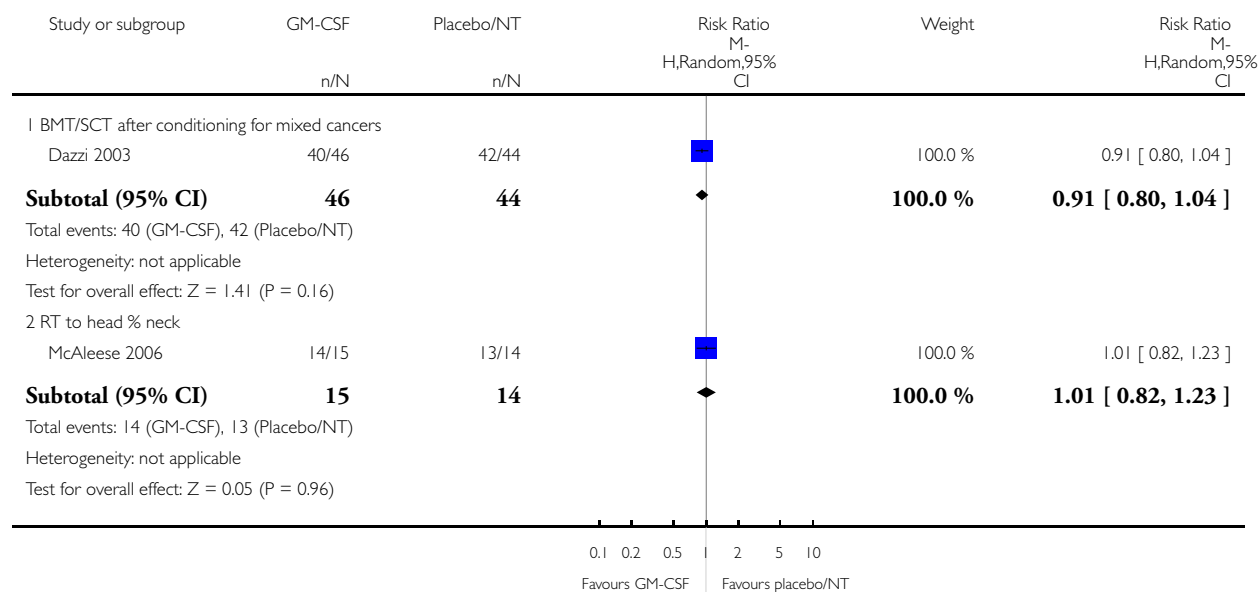


Analysis 4.1. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 1 Oral mucositis (any).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 4 GM-CSF versus placebo/no treatment

Outcome: 1 Oral mucositis (any)

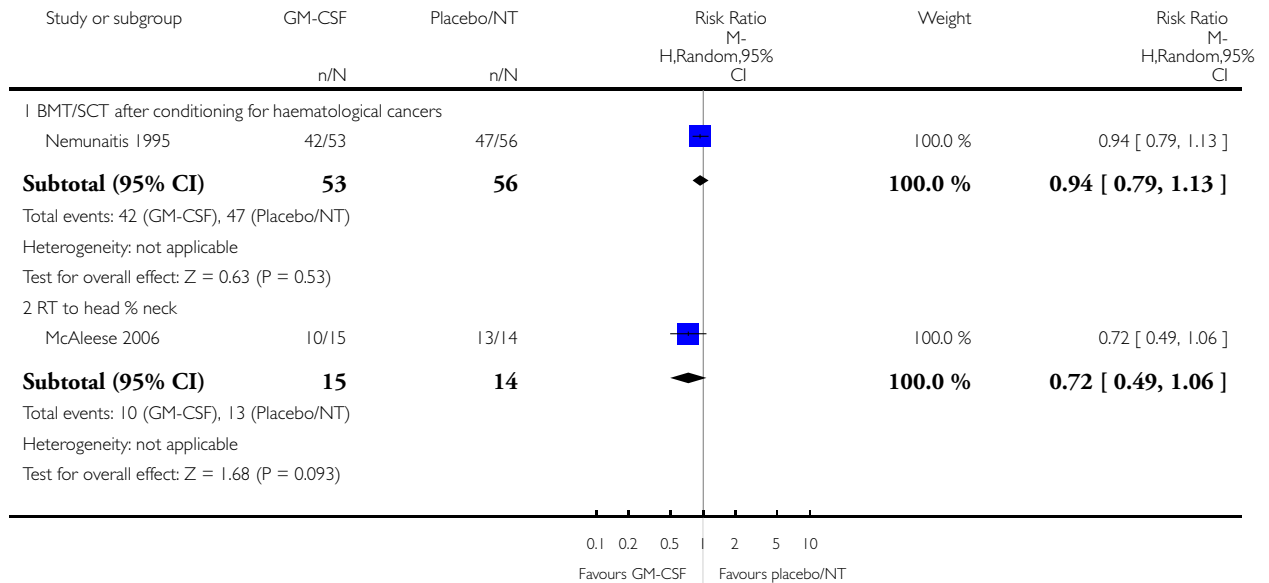


Analysis 4.2. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 2 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 4 GM-CSF versus placebo/no treatment

Outcome: 2 Oral mucositis (moderate + severe)

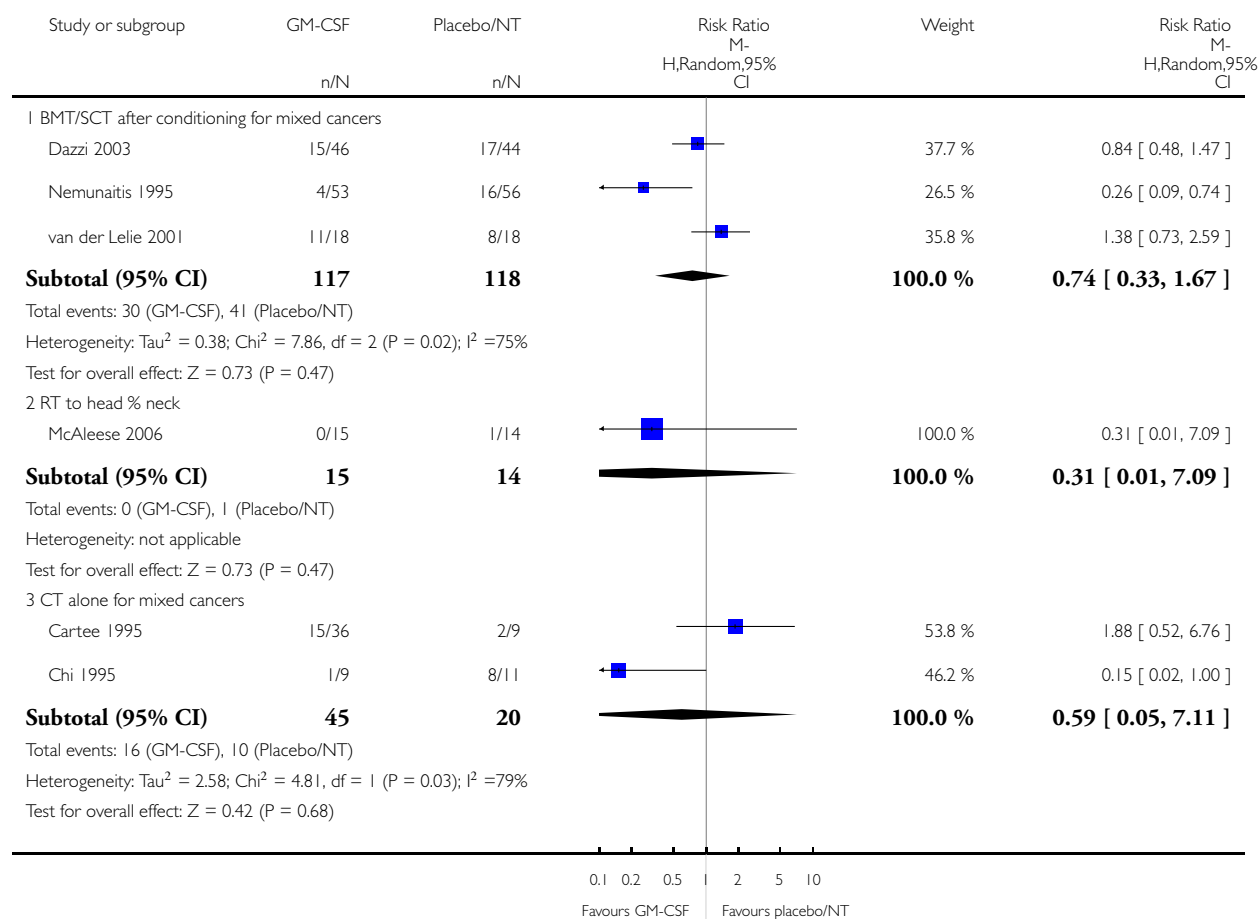


Analysis 4.3. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 3 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 4 GM-CSF versus placebo/no treatment

Outcome: 3 Oral mucositis (severe)

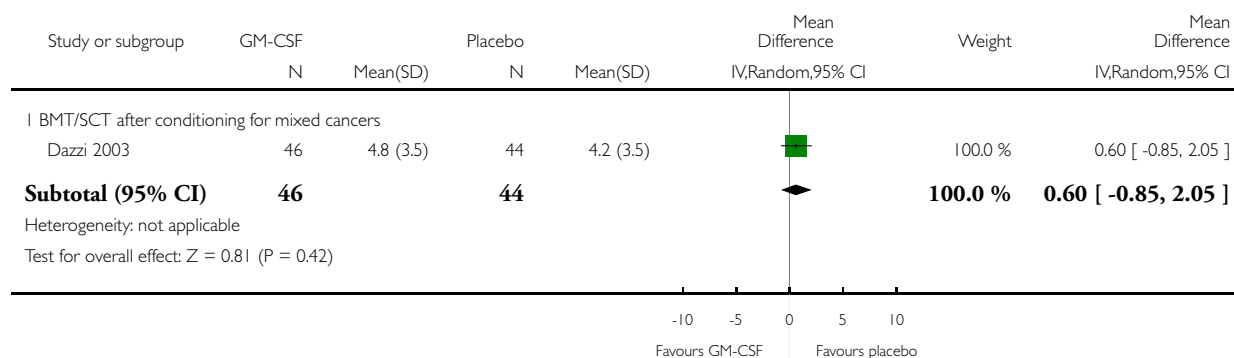


Analysis 4.4. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 4 Oral pain (maximum score on 0 to 10 VAS).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 4 GM-CSF versus placebo/no treatment

Outcome: 4 Oral pain (maximum score on 0 to 10 VAS)

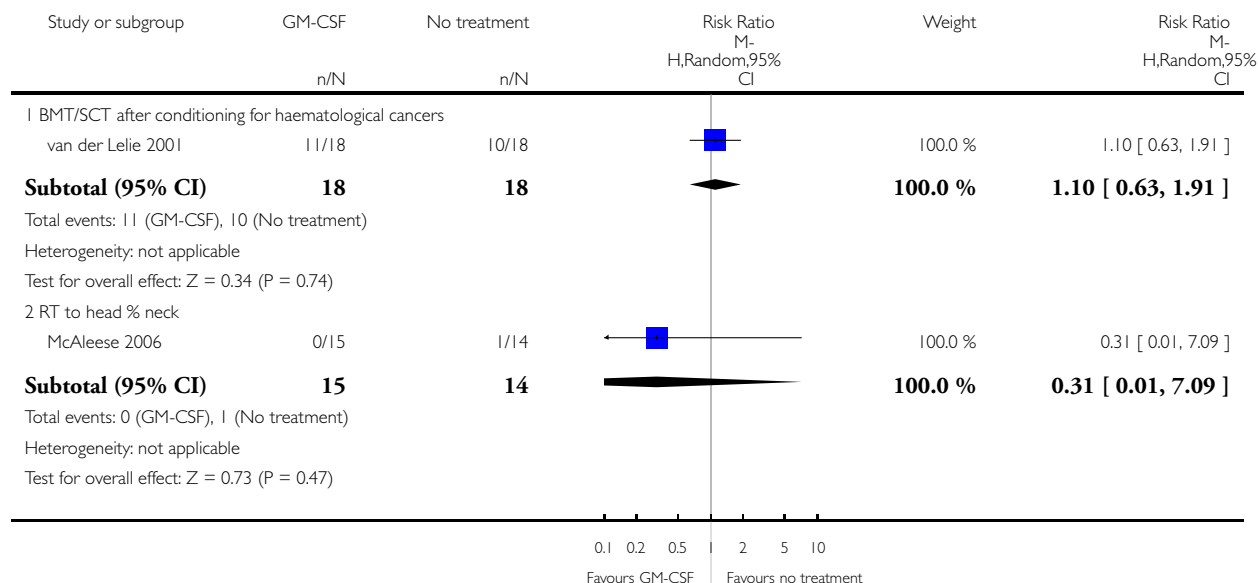


Analysis 4.5. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 5 Normalcy of diet (use of feeding tube/parenteral nutrition).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 4 GM-CSF versus placebo/no treatment

Outcome: 5 Normalcy of diet (use of feeding tube/parenteral nutrition)

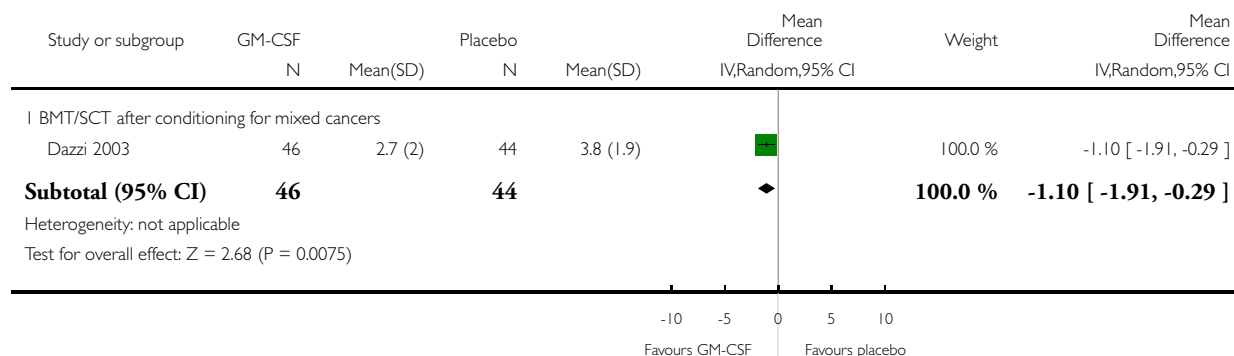


Analysis 4.6. Comparison 4 GM-CSF versus placebo/no treatment, Outcome 6 Number of days of treatment with opioid analgesics.

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 4 GM-CSF versus placebo/no treatment

Outcome: 6 Number of days of treatment with opioid analgesics

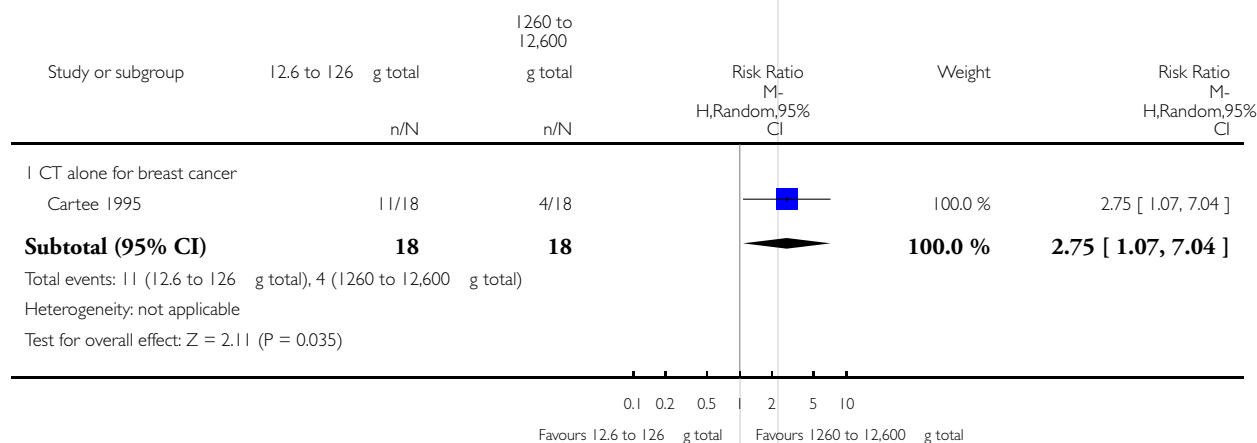


Analysis 5.1. Comparison 5 GM-CSF (dose comparison), Outcome 1 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 5 GM-CSF (dose comparison)

Outcome: 1 Oral mucositis (severe)

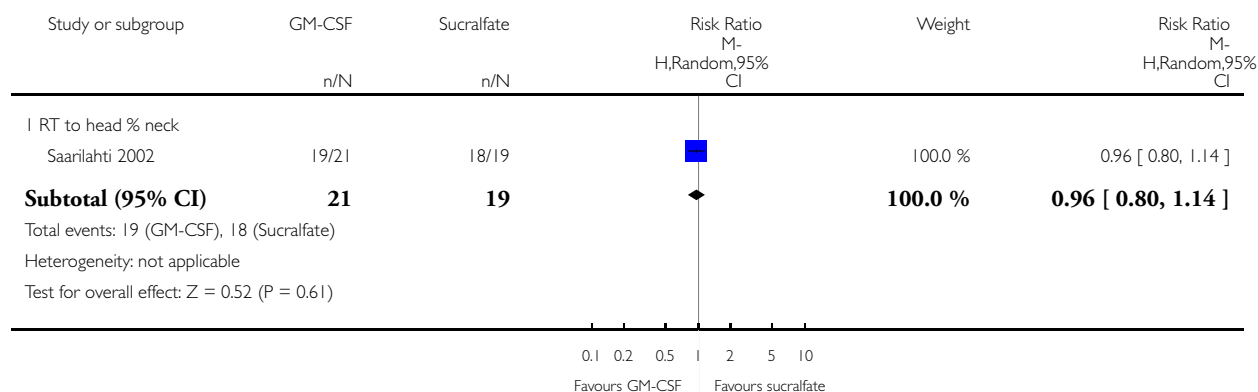


Analysis 6.1. Comparison 6 GM-CSF versus sucralfate, Outcome 1 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 6 GM-CSF versus sucralfate

Outcome: 1 Oral mucositis (moderate + severe)

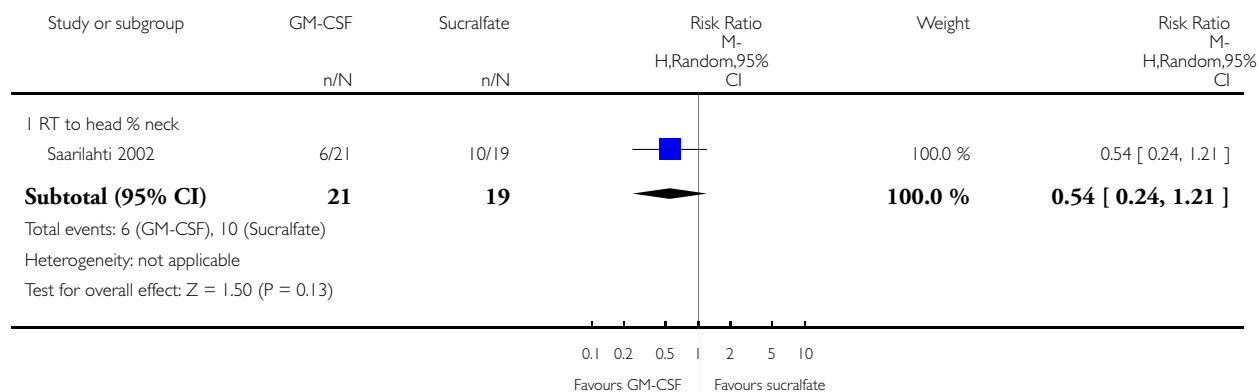


Analysis 6.2. Comparison 6 GM-CSF versus sucralfate, Outcome 2 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 6 GM-CSF versus sucralfate

Outcome: 2 Oral mucositis (severe)

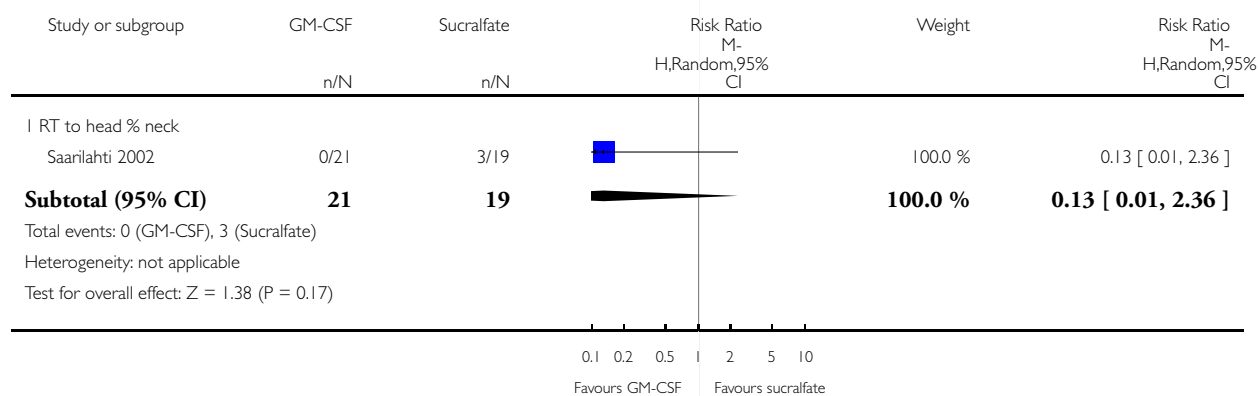


Analysis 6.3. Comparison 6 GM-CSF versus sucralfate, Outcome 3 Interruptions to cancer treatment.

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 6 GM-CSF versus sucralfate

Outcome: 3 Interruptions to cancer treatment

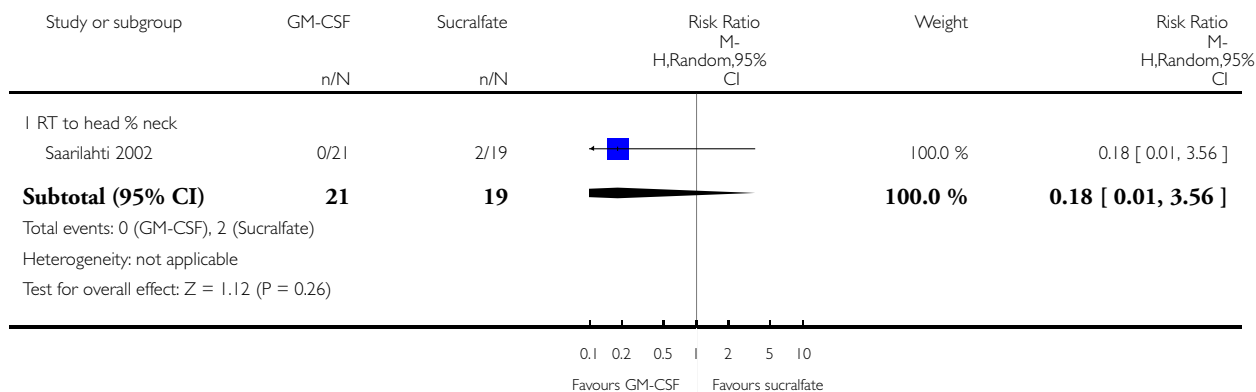


Analysis 6.4. Comparison 6 GM-CSF versus sucralfate, Outcome 4 Normalcy of diet (use of PEG tube).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 6 GM-CSF versus sucralfate

Outcome: 4 Normalcy of diet (use of PEG tube)

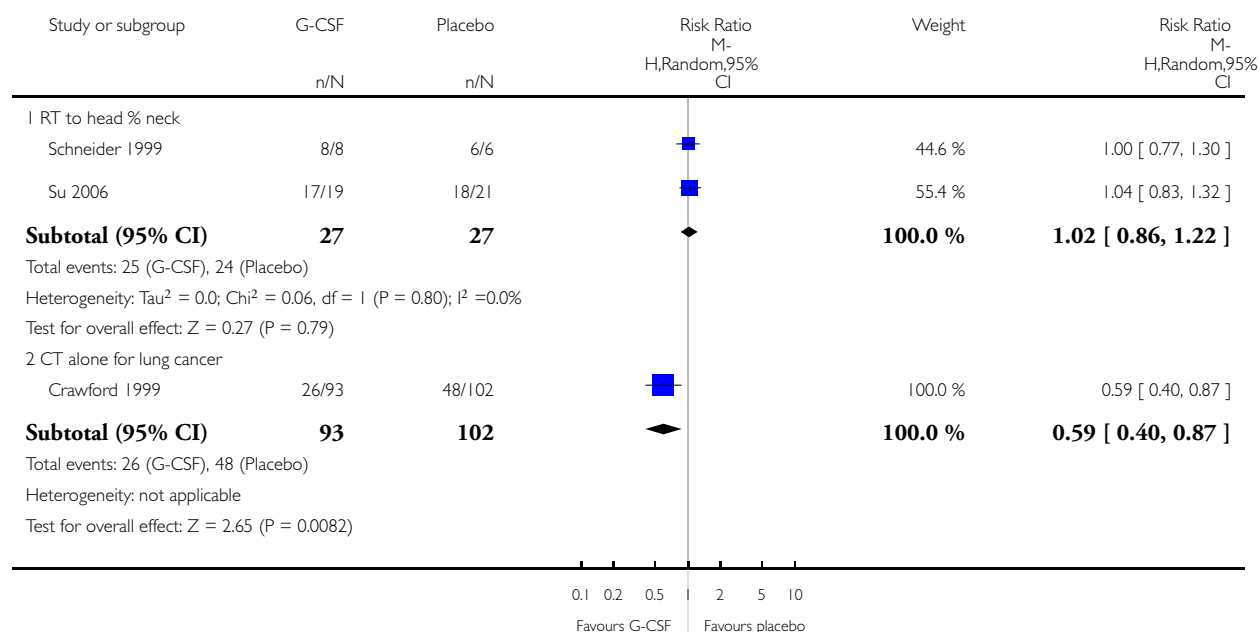


Analysis 7.1. Comparison 7 G-CSF versus placebo/no treatment, Outcome 1 Oral mucositis (any).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 7 G-CSF versus placebo/no treatment

Outcome: 1 Oral mucositis (any)

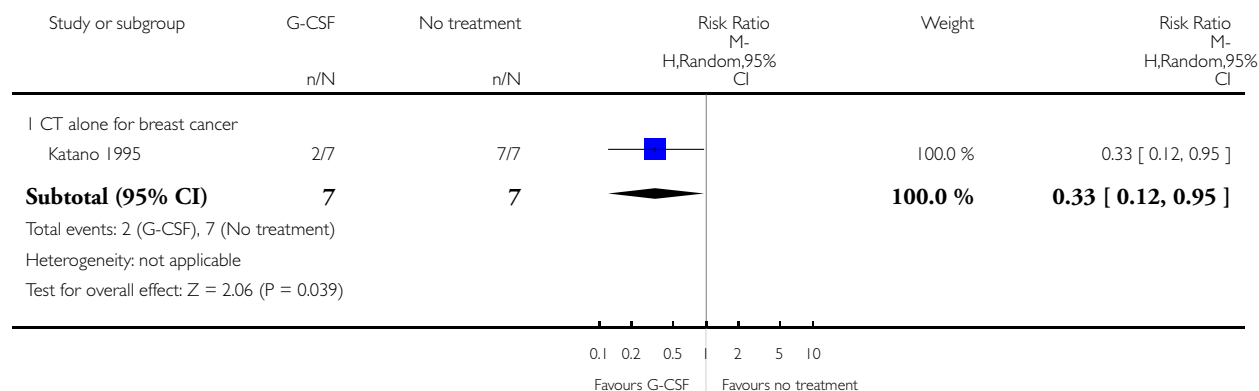


Analysis 7.2. Comparison 7 G-CSF versus placebo/no treatment, Outcome 2 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 7 G-CSF versus placebo/no treatment

Outcome: 2 Oral mucositis (moderate + severe)

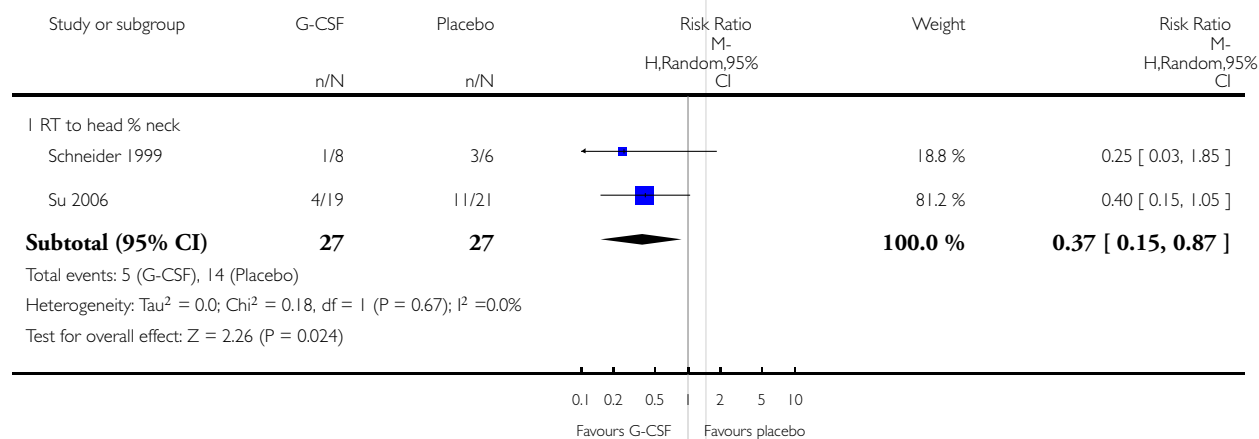


Analysis 7.3. Comparison 7 G-CSF versus placebo/no treatment, Outcome 3 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 7 G-CSF versus placebo/no treatment

Outcome: 3 Oral mucositis (severe)

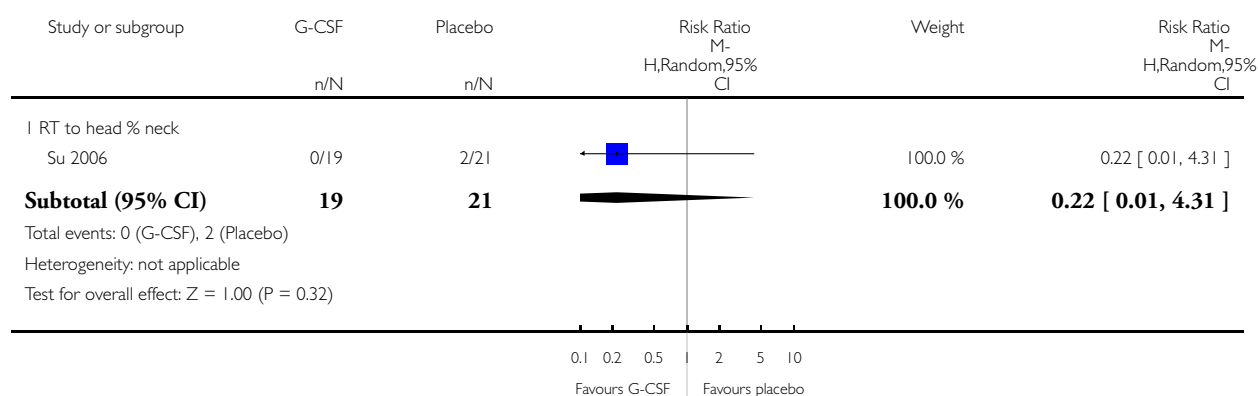


Analysis 7.4. Comparison 7 G-CSF versus placebo/no treatment, Outcome 4 Interruptions to cancer treatment (RT interruption).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 7 G-CSF versus placebo/no treatment

Outcome: 4 Interruptions to cancer treatment (RT interruption)

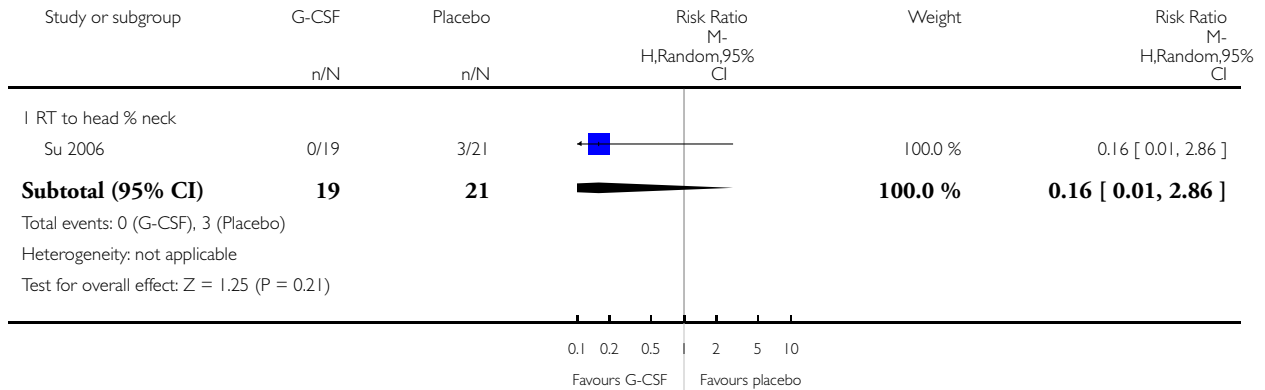


Analysis 7.5. Comparison 7 G-CSF versus placebo/no treatment, Outcome 5 Normalcy of diet (use of PEG tube).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 7 G-CSF versus placebo/no treatment

Outcome: 5 Normalcy of diet (use of PEG tube)

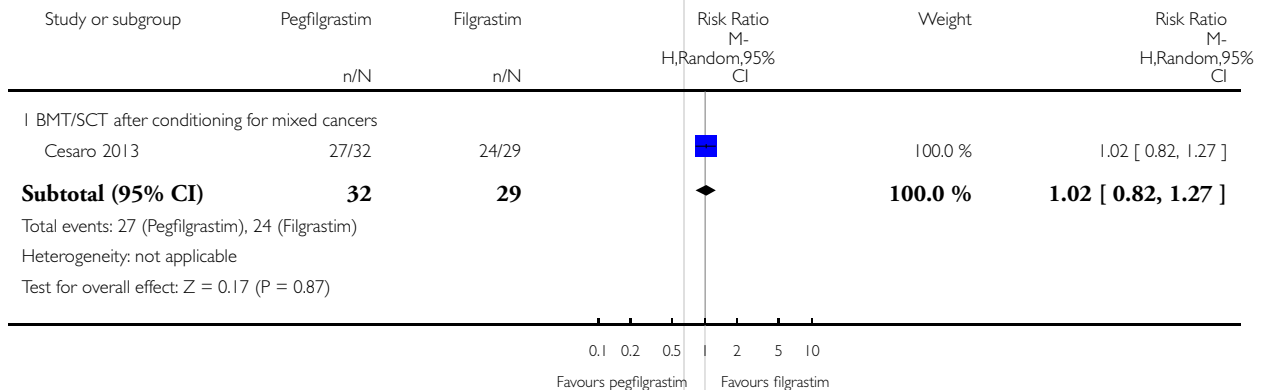


Analysis 8.1. Comparison 8 G-CSF (pegfilgrastim) versus G-CSF (filgrastim), Outcome 1 Oral mucositis (any).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 8 G-CSF (pegfilgrastim) versus G-CSF (filgrastim)

Outcome: 1 Oral mucositis (any)

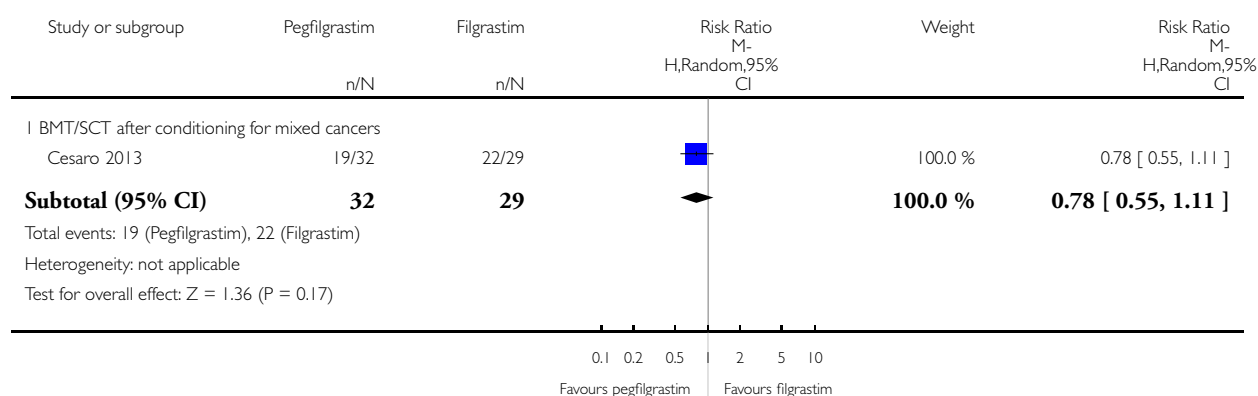


Analysis 8.2. Comparison 8 G-CSF (pegfilgrastim) versus G-CSF (filgrastim), Outcome 2 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 8 G-CSF (pegfilgrastim) versus G-CSF (filgrastim)

Outcome: 2 Oral mucositis (moderate + severe)

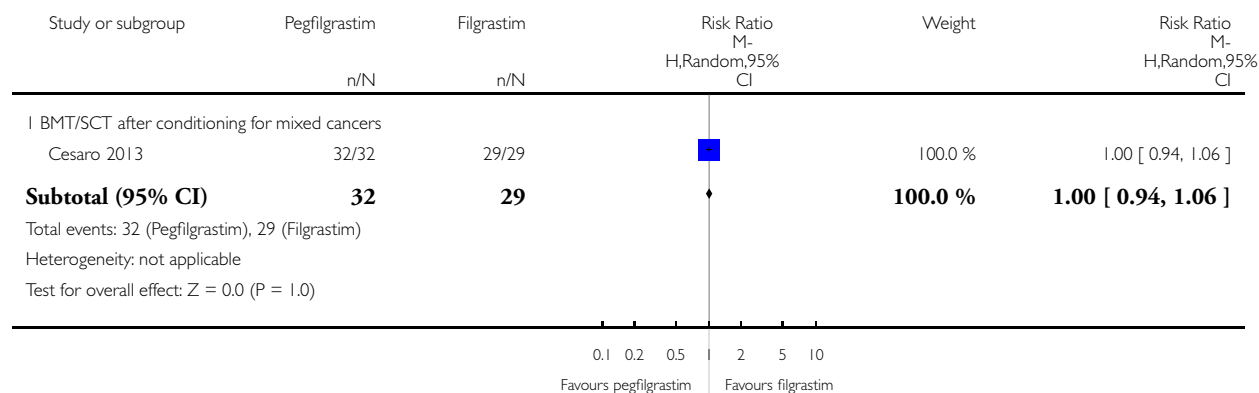


Analysis 8.3. Comparison 8 G-CSF (pegfilgrastim) versus G-CSF (filgrastim), Outcome 3 Normalcy of diet (use of supplemental nutrition).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 8 G-CSF (pegfilgrastim) versus G-CSF (filgrastim)

Outcome: 3 Normalcy of diet (use of supplemental nutrition)

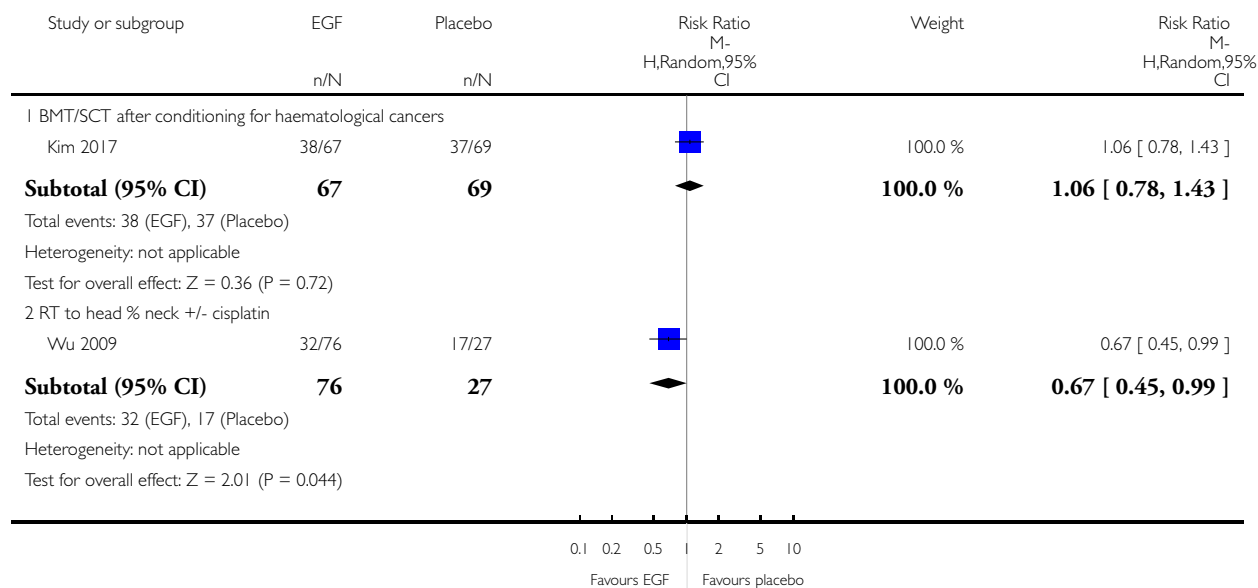


Analysis 9.1. Comparison 9 EGF versus placebo, Outcome 1 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 9 EGF versus placebo

Outcome: 1 Oral mucositis (moderate + severe)

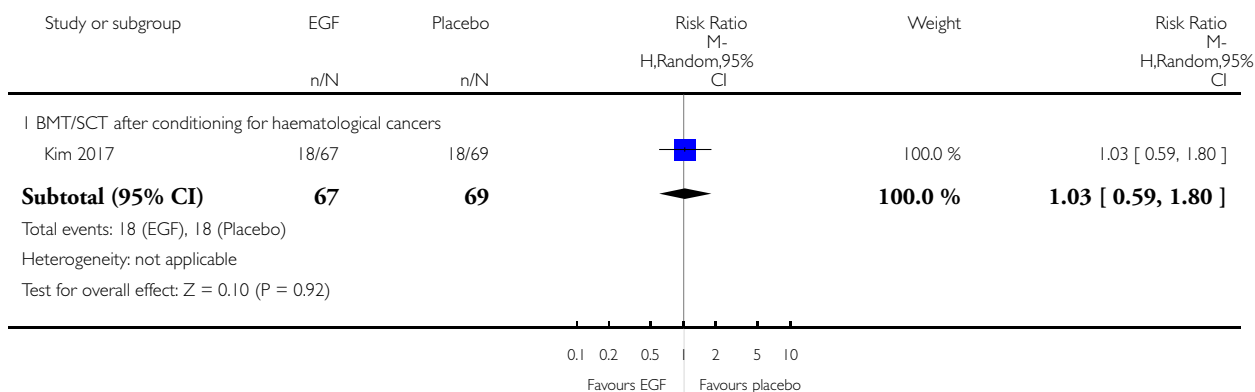


Analysis 9.2. Comparison 9 EGF versus placebo, Outcome 2 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 9 EGF versus placebo

Outcome: 2 Oral mucositis (severe)

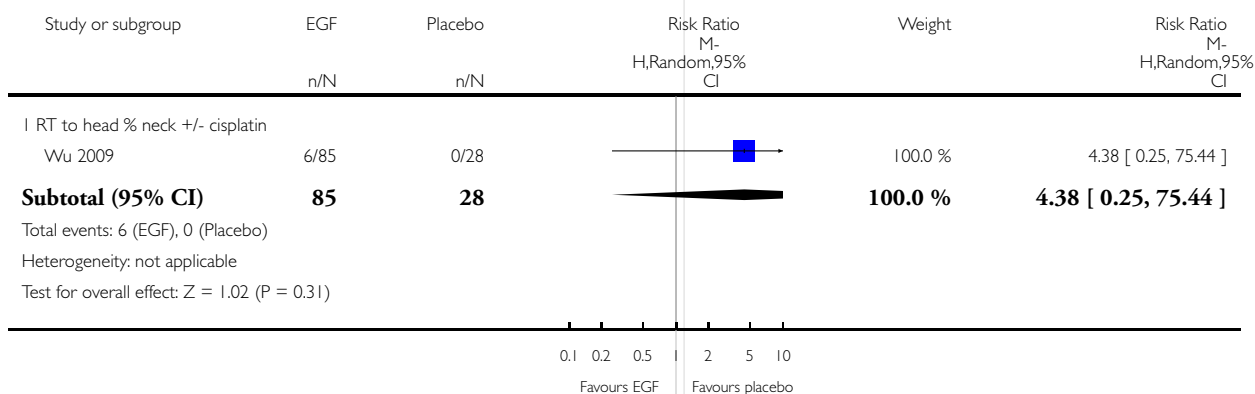


Analysis 9.3. Comparison 9 EGF versus placebo, Outcome 3 Interruptions to cancer treatment (RT breaks > 2 consecutive days).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 9 EGF versus placebo

Outcome: 3 Interruptions to cancer treatment (RT breaks > 2 consecutive days)

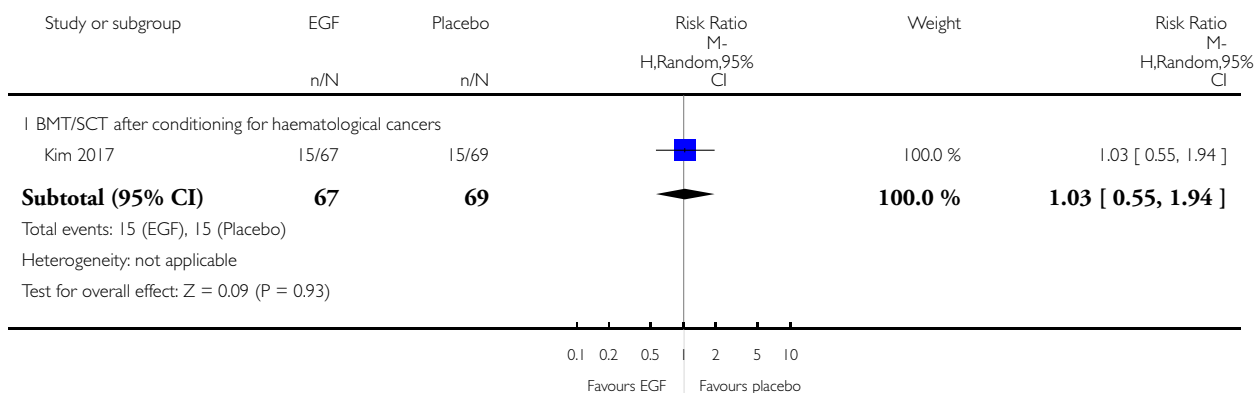


Analysis 9.4. Comparison 9 EGF versus placebo, Outcome 4 Normalcy of diet (use of supplemental nutrition).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 9 EGF versus placebo

Outcome: 4 Normalcy of diet (use of supplemental nutrition)

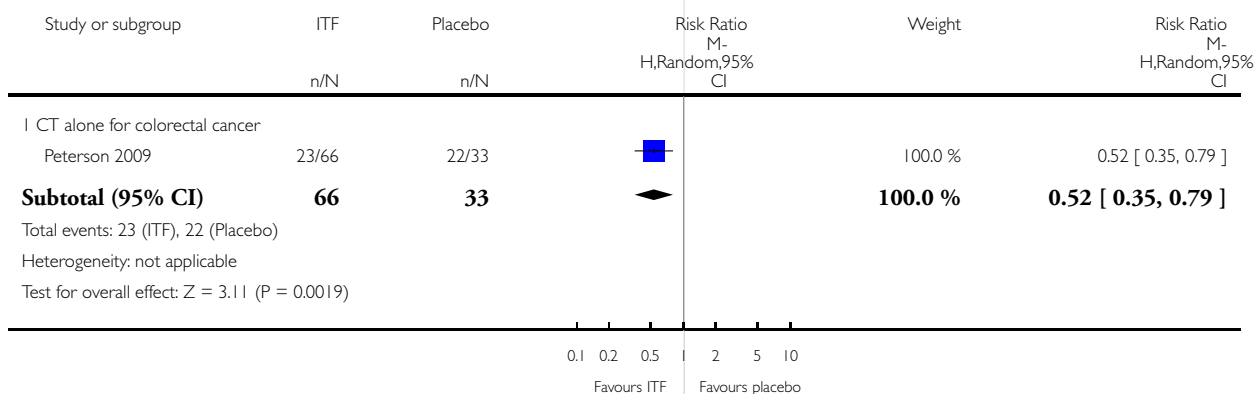


Analysis 10.1. Comparison 10 ITF versus placebo, Outcome 1 Oral mucositis (any).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 10 ITF versus placebo

Outcome: 1 Oral mucositis (any)

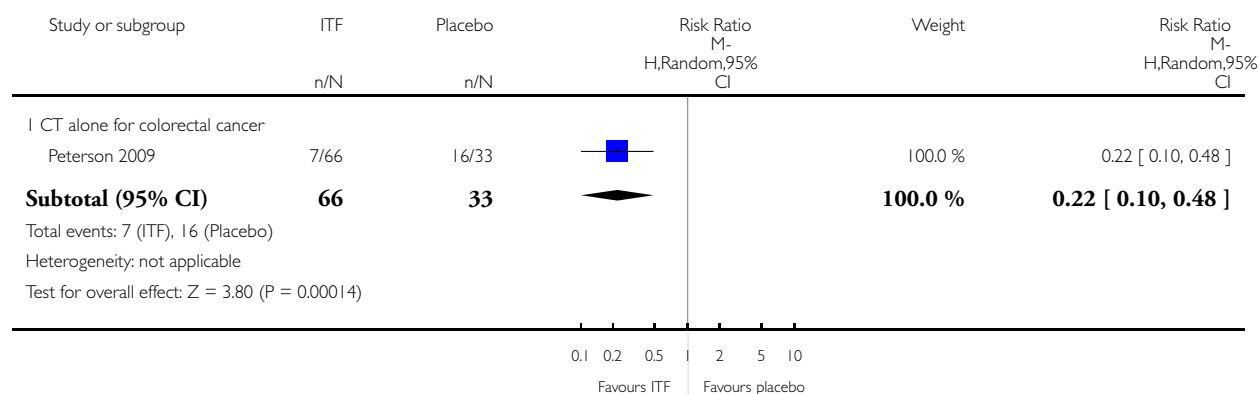


Analysis 10.2. Comparison 10 ITF versus placebo, Outcome 2 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 10 ITF versus placebo

Outcome: 2 Oral mucositis (moderate + severe)

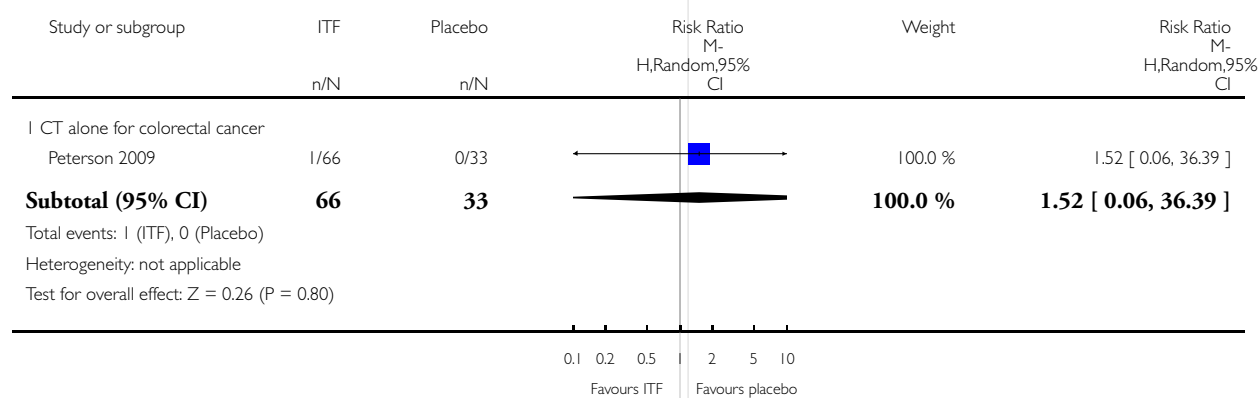


Analysis 10.3. Comparison 10 ITF versus placebo, Outcome 3 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 10 ITF versus placebo

Outcome: 3 Oral mucositis (severe)

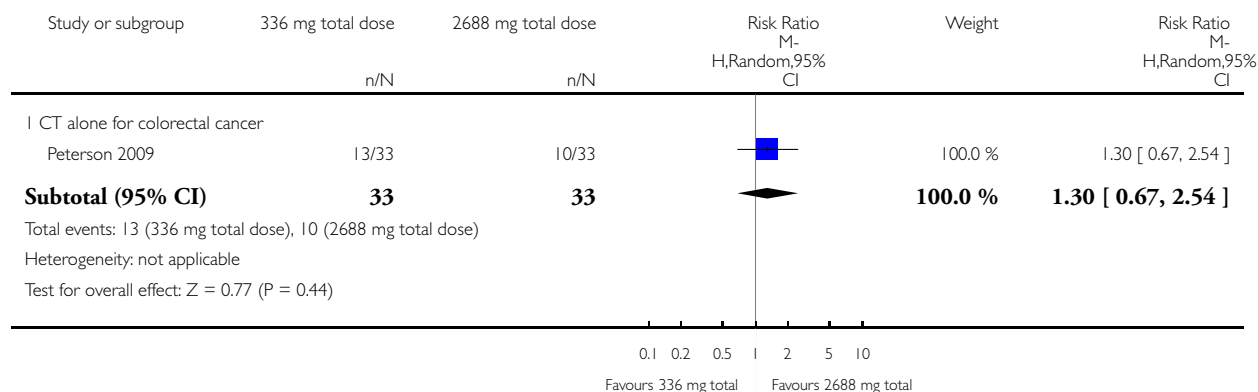


Analysis 11.1. Comparison 11 ITF (dose comparison), Outcome 1 Oral mucositis (any).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 11 ITF (dose comparison)

Outcome: 1 Oral mucositis (any)

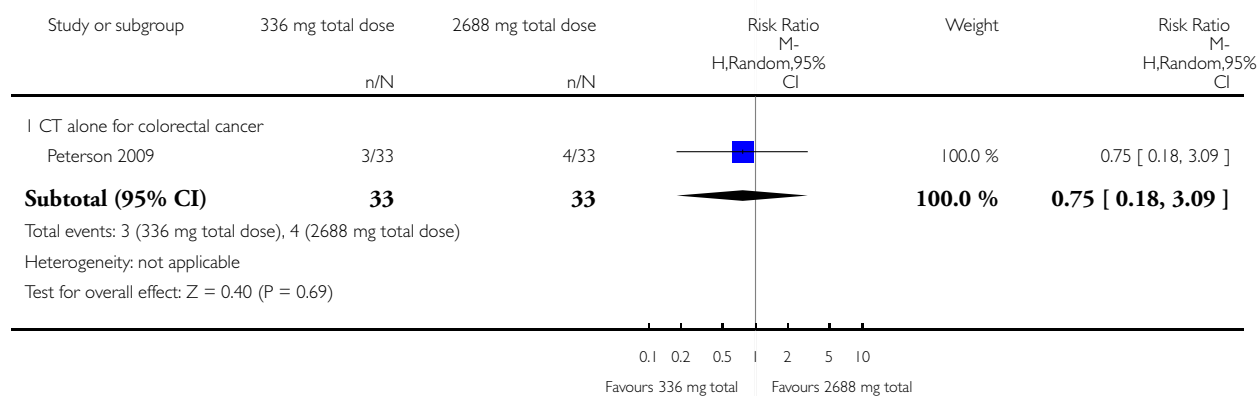


Analysis 11.2. Comparison 11 ITF (dose comparison), Outcome 2 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 11 ITF (dose comparison)

Outcome: 2 Oral mucositis (moderate + severe)

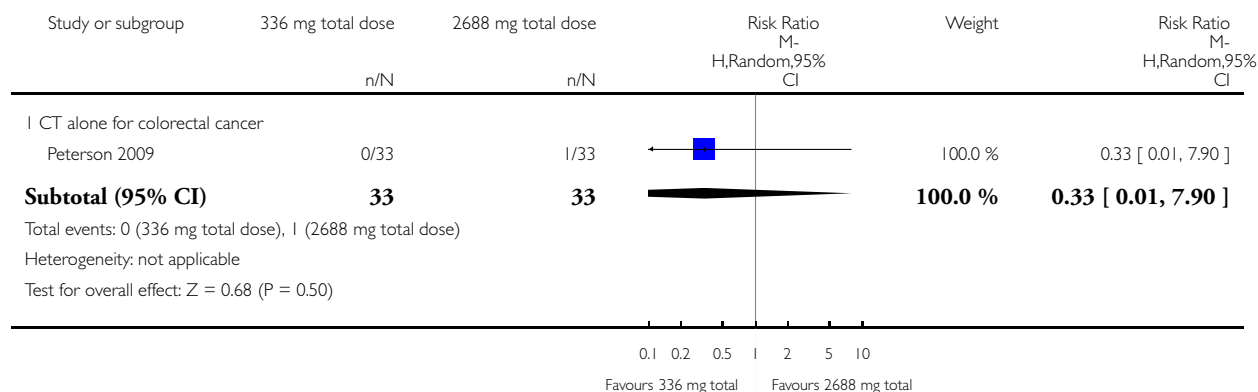


Analysis 11.3. Comparison 11 ITF (dose comparison), Outcome 3 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 11 ITF (dose comparison)

Outcome: 3 Oral mucositis (severe)

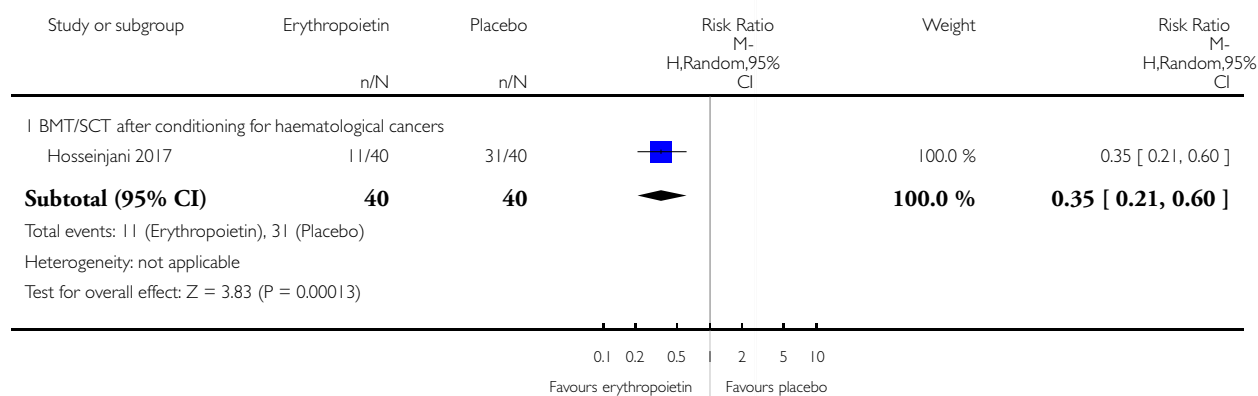


Analysis 12.1. Comparison 12 Erythropoietin versus placebo, Outcome 1 Oral mucositis (any).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 12 Erythropoietin versus placebo

Outcome: 1 Oral mucositis (any)

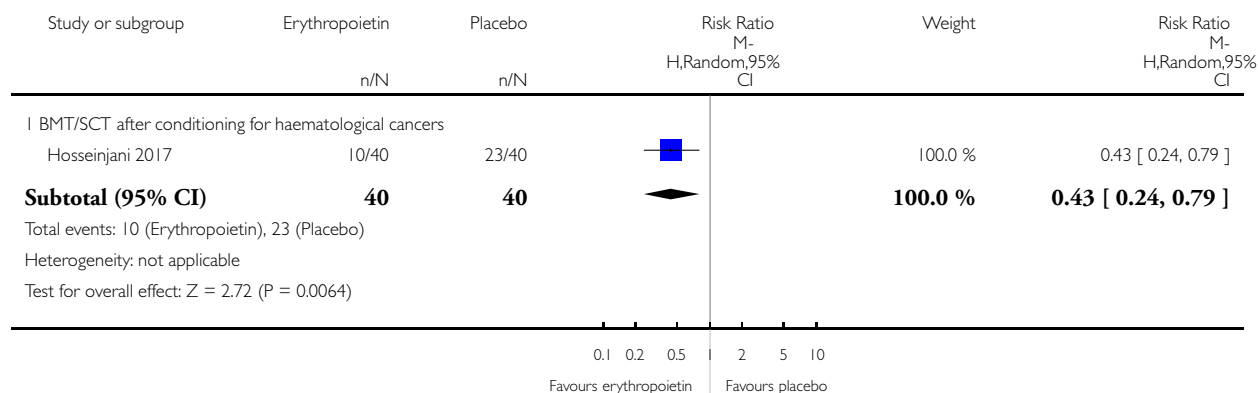


Analysis 12.2. Comparison 12 Erythropoietin versus placebo, Outcome 2 Oral mucositis (moderate + severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 12 Erythropoietin versus placebo

Outcome: 2 Oral mucositis (moderate + severe)

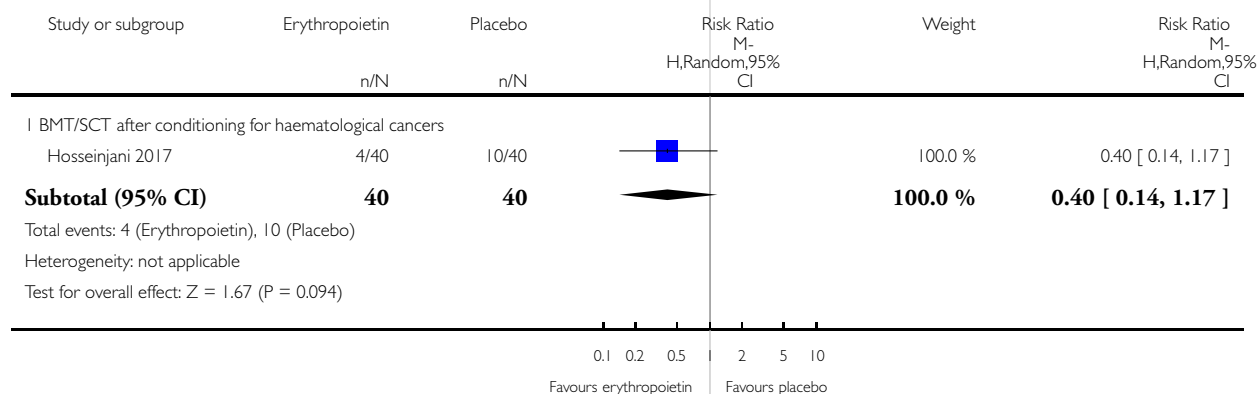


Analysis 12.3. Comparison 12 Erythropoietin versus placebo, Outcome 3 Oral mucositis (severe).

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 12 Erythropoietin versus placebo

Outcome: 3 Oral mucositis (severe)

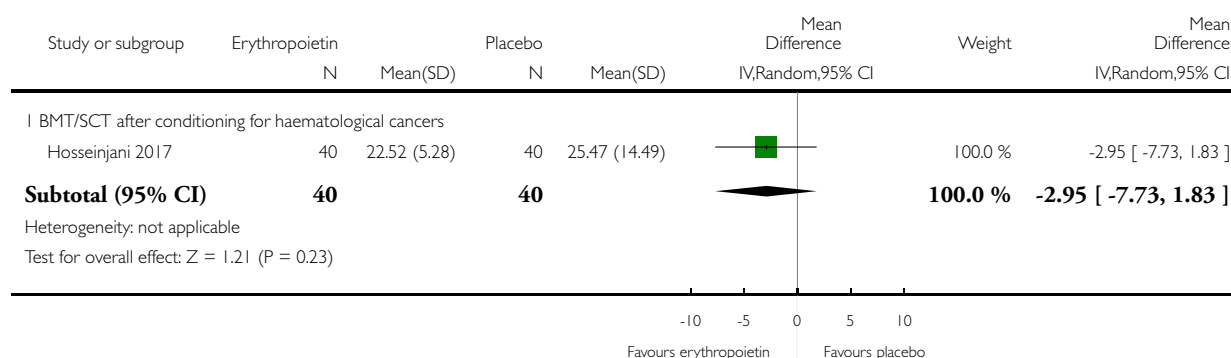


Analysis 12.4. Comparison 12 Erythropoietin versus placebo, Outcome 4 Number of days in hospital.

Review: Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors

Comparison: 12 Erythropoietin versus placebo

Outcome: 4 Number of days in hospital



ADDITIONAL TABLES

Table 1. Adverse events: KGF

Study ID	Adverse events results
Blazar 2006	<ul style="list-style-type: none"> • AEs with incidence $\geq 10\%$ greater in KGF group: higher rate of skin rash in KGF group (65/69 versus 21/31; RR 1.39, 95% CI 1.08 to 1.79; $P = 0.01$). Insufficient evidence of a difference in edema, infection, or local pain • Grade 3 to 4 (WHO and NCI-CTC 0 to 4 toxicities scales) AEs with higher incidence in KGF group: insufficient evidence of a difference in skin reactions, diarrhoea, local pain, or cardiac events
Blijlevens 2013	<ul style="list-style-type: none"> • KGF-related AE (NCI-CTC): higher rate in KGF group (141/220 versus 17/57; RR 2.15, 95% CI 1.43 to 3.24; $P = 0.0003$) • KGF-related serious AE (no definition of 'serious' given) (NCI-CTC): insufficient evidence of a difference (4/220 versus 0/57; $P = 0.56$) • KGF-related severe AE (NCI-CTC grade 3, 4 or 5) (grade 5 = death): insufficient evidence of a difference (23/220 versus 0/57; $P = 0.08$)
Bradstock 2014	Insufficient evidence of a difference in infection or Grade 3 to 4 (NCI-CTC 0 to 4 toxicity scale) skin rash/desquamation
Brizel 2008	The study authors state that most adverse events were considered to be caused by the cancer treatment or the underlying cancer itself and not related to study treatment. 2 participants in the palifermin group had serious adverse events considered to be related to the intervention: 1 had increased sputum production; the other had dehydration, dysphagia, pain (including abdominal), pancreatitis, and subsequently had schistosomiasis

Table 1. Adverse events: KGF (Continued)

Fink 2011	<p>Total of 28 side effects in palifermin group occurring in 11 of 22 patients (50%) who received at least 4 of the 6 doses. Most frequent (90.9%) were cases of erythema or exanthema, often associated with itching (54.5%) . Often (54.5%) a swelling of the oral mucosa including the tongue occurred. In 4 out of 6 patients, this was accompanied by taste disturbance. The severity of side effects were classified as mild to moderate. The CTC Grade 3 occurred only once in the form of a strong heat sensation</p> <p>In 1 of the 11 cases, there was premature discontinuation of palifermin due to severe facial swelling with eyelid and laryngeal pain as well as painful swelling of the hands following the second injection</p>
Freytes 2004	<p>25 different adverse events were reported and were mostly not KGF-related. There was insufficient evidence of a difference for diarrhoea, abdominal pain, infection or rash</p>
Gholizadeh 2016	<p>“..two patients reported knee joint pain, skin rash was observed in one patient, two patients had abnormal taste, and one showed lingual mucosal thickening” (control group was chlorhexidine mouthrinse. The authors do not report the events by treatment group)</p>
Henke 2011	<ul style="list-style-type: none"> • “Initially, patients were allocated to three arms: palifermin (180 g/kg/wk) throughout radiochemotherapy (ie, for at least seven doses); palifermin (180 g/kg/wk) for four doses and then placebo throughout the remainder of radiochemotherapy; or placebo throughout radiochemotherapy. However, after one serious adverse event of respiratory insufficiency was reported in one of the first 10 patients, the data monitoring committee concluded that the study should be restarted with a lower palifermin dose (120 g/kg/wk)” • “Most patients (97%) experienced at least one adverse event.....One serious adverse event (febrile neutropenia) considered related to study drug was reported for one patient in the palifermin arm”
Jagasia 2012	<p>KGF-related AEs with incidence $\geq 5\%$ in KGF group: higher rate of gastrointestinal disorders in KGF group (18/78 versus 2/73; RR 8.42, 95% CI 2.02 to 35.04; P = 0.003). Insufficient evidence of a difference in any AE, tongue coating, tongue disorder, skin and subcutaneous tissue disorders, rash, pruritus, or erythema</p>
Le 2011	<p>“Study drug-related AEs were reported for 35% of palifermin and 11% of placebo patients. The most frequent study drug-related AEs (palifermin, placebo) were rash (9%, 2%), flushing (5%, 0%), dysgeusia (5%, 1%), nausea (4%, 1%),and vomiting (3%, 1%). None of these events led to study withdrawal. Serious AEs considered related to study treatment were reported for five palifermin patients (5%; one each with necrotic pancreatitis, hypersensitivity, tracheostomy malfunction, peritoneal carcinoma, and convulsion) and two placebo patients (2%; one each with hepatitis/hepatic enzyme increase and cryptogenic organizing pneumonia)”</p>
Lucchese 2016a	<p>“The administration of palifermin was generally safe and without considerable complications. The only adverse reactions were rashes (lasting for 48-72 hours) localized to the face, upper neck and shoulders, erythema, and altered taste (consistent with the pharmacologic action of palifermin of oral epithelium and skin), most of which were of NCI grade 1 or 2 severity”</p>
Lucchese 2016b	<p>“The administration of palifermin was mostly safe and without substantial complications. The mean duration of the OM and the number of adverse event was significant less in the palifermin group (Tables II, III, Figure 1). The main adverse episodes were erythema, cutaneous rashes and altered taste and three of the patients in the palifermin group showed a light thickness of the tongue, mouth and palate”</p>
Meropol 2003	<p>“Although the predefined frequency of DLTs attributable to KGF was not reached with KGF doses between 1 and 80 $\mu\text{g/kg/d}$, there were three adverse reactions involving the skin that required discontinuation of KGF in the 18 patients treated with 60 or 80 $\mu\text{g/kg}$ (Table 5). Overall, skin and oral adverse events (rash, flushing, pruritus, edema, hypoesthesia, paresthesia, tongue disorder [thickening], and alteration in taste sensation) attributed to</p>

Table 1. Adverse events: KGF (Continued)

	<p>KGF occurred in 13 of 18 patients treated with 60 and 80 µg/kg of KGF (eight patients, grade 1; four patients, grade 2; and one patient, grade 3) and in three of 11 patients treated with 40 µg/kg (all grade 1). These events were reported in 16 of 39 patients (41%) dosed with KGF at > 20 µg/kg/d, whereas these symptoms were reported in only two of 21 subjects (10%) treated with placebo. The skin and oral toxicities associated with KGF were generally mild to moderate in severity, with onset approximately 36 hours after the first dose of KGF and resolution 7 to 10 days thereafter”</p>
Rosen 2006	<ul style="list-style-type: none"> • “As expected based on the pharmacologic activity of palifermin, oral-related AEs were reported more frequently in palifermin than in patients receiving placebo (Table 3). During cycle 1, 50% of patients receiving palifermin experienced an oral-related AE, compared with 33% of patients receiving placebo (P = 0.13). Similarly, 56% of patients receiving palifermin during the second chemotherapy cycle had at least one oral-related AE, compared with 38% of patients receiving placebo (P = 0.26). The overall incidences of skin-related AEs, reported as a palifermin-related AE in other clinical settings, were comparable between the two treatment groups (Table 3). During cycle 1, skin-related AEs were 56% in the placebo group versus 43% in patients receiving palifermin. During cycle 2, these incidences between the two groups were comparable (palifermin, 52%; placebo, 50%)” • There were no serious KGF-related AEs in either group and either cycle
Spielberger 2004	<p>“The incidence, frequency, and severity of adverse events were similar in the two groups, and most were attributable to the underlying cancer, cytotoxic chemotherapy, or total-body irradiation. Those that occurred with an incidence that was at least 5 percentage points higher in the palifermin group than in the placebo group are listed in Table 3. Most of these adverse events were consistent with the pharmacologic action of palifermin on skin and oral epithelium (e.g., rash, pruritus, erythema, paresthesia, mouth and tongue disorders, and taste alteration). All these events were mild to moderate in severity, transient (occurring approximately three days after the third dose of palifermin and lasting approximately three days), and not a cause for the discontinuation of study drug. Serious adverse events considered to be related to treatment occurred in one palifermin recipient (rash) and one placebo recipient (hypotension)”</p>
Vadhan-Raj 2010	<ul style="list-style-type: none"> • “Many patients who received palifermin sensed thickening of the oral mucosa and tongue” (first 2 blinded cycles: 72% versus 31%, P = 0.007) • “Treatment with palifermin was well tolerated. Table 3 shows the common adverse effects that occurred during the first 2 blinded cycles, which included symptoms of thickness of oral mucosa, tongue, and lips (Figure 4); altered taste; flushing; warm sensation; and increased saliva. These adverse effects were mild to moderate and transient in nature. Similar side effects were observed during later cycles...but they did not worsen in severity”

AE = adverse event; CI = confidence interval; KGF = keratinocyte growth factor; NCI-CTC = National Cancer Institute common toxicity criteria; RR = risk ratio; WHO = World Health Organization.

Table 2. Adverse events: GM-CSF

Study ID	Adverse events results
Cartee 1995	<p>2 participants (group allocation not reported) withdrew by day 3 due to intolerance to their mouthwash (dry mouth); 1 participant receiving GM-CSF (1 µg/mL) had mouthwash withdrawn by day 3 due to possible allergic reaction (sensation of fullness in the posterior pharyngeal area) but resolved within 4 hours (the participant was withdrawn but appears to have been included in the analysis)</p>

Table 2. Adverse events: GM-CSF (Continued)

Chi 1995	"One patient had fever and chills, and two patients had general malaise and headache during GM-CSF treatment. No patient had evidence of fluid retention after GM-CSF"
Dazzi 2003	Not reported
Makkonen 2000	(Sucralfate given to both groups) "Only 2 of the 20 patients treated with GM-CSF and sucralfate did not experience any side effects related to the drugs, but most side effects were mild (WHO Grade 1 or 2). The most common side effects were local skin reactions, fever, bone pain, and mild nausea...In the control group only 1 patient complained of nausea possibly related to the use of sucralfate, and another patient interrupted sucralfate treatment because of the same reason"
McAleese 2006	"12 patients who received GM-CSF had elevated white cell counts (WCC). The range of maximal WCC was 7.2-30.5 (median 19.7). All WCC had returned to normal within 3 weeks of completing injections (median 2 weeks). Three patients developed influenza-like symptoms with the GM-CSF and in one patient the injections were stopped because of this symptom. One patient developed an erythematous rash at his injection sites after completing his course of 14 injections (Figure 3). He had a past history of allergy to radiographic contrast medium"
Nemunaitis 1995	<ul style="list-style-type: none"> • "The incidences of grades III or IV toxicities between rhGM-CSF or placebo occurring with a > 10% frequency included anorexia (38% vs. 36%), nausea (26% vs. 29%), diarrhea (19% vs. 7%), stomatitis (19% vs. 14%) and hypertension (13% vs. 20%)" • "The following events were reported with higher frequency in the rhGM-CSF group compared with placebo: diarrhea (81% vs. 66%), bone pain (21% vs. 5%), abdominal pain (38% vs. 23%), vomiting (70% vs. 57%), pharyngitis (23% vs. 13%), pruritis (23% vs. 13%) and ocular hemorrhage (11% vs. 0%)" • "Placebo-treated patients had higher occurrence of unspecified pain (36% vs. 17%), back pain (18% vs. 9%), peripheral edema (21% vs. 15%), hematuria (21% vs. 9%) and pneumonia (7% vs. 0%)"
Saarilahti 2002	(Comparator was sucralfate) "Both mouthwashes were well tolerated, and none of the patients reported any adverse effects related to the mouthwashes. Adverse effects commonly associated with subcutaneous GM-CSF administration, such as nausea, vomiting, bone pain, headaches, and fever, were not observed"
van der Lelie 2001	Not reported

GM-CSF = granulocyte-macrophage colony-stimulating factor.

Table 3. G-CSF versus placebo

Study ID	Population	Outcome	GM-CSF	Placebo	Result
Linch 1993	BMT/SCT after conditioning for haematological cancers	Oral mucositis: no scale described	No data	No data	"There was no difference in the frequency of stomatitis (defined as a sore, infected or ulcerated mouth, lips or pharynx), the incidence being between 29 and 33% in all groups"

BMT = bone marrow transplantation; G-CSF: granulocyte-colony stimulating factor; SCT = stem cell transplantation.

Table 4. Adverse events: G-CSF

Study ID	Adverse events results
Cesaro 2013	"Both pegfilgrastim and filgrastim were well tolerated and no significant adverse effects were associated with their use" (G-CSF versus G-CSF)
Crawford 1999	Approximately 20% of participants receiving G-CSF experienced mild to moderate skeletal pain which was resolved by using oral analgesics; 6% of participants in both groups reported mild generalised rash/itching; 3 participants experienced an event thought to be G-CSF-related and which caused them to request withdrawal from the study: abdominal pain, diffuse aches and pains, and a flare-up of pre-existing eczema
Katano 1995	Not reported
Linch 1993	"There was no difference in the overall frequency of adverse clinical or laboratory events between the groups or in the frequency of adverse events thought by the clinicians to be possibly or probably due to study medication"
Schneider 1999	Not reported
Su 2006	"In general, toxicities typical of postoperative RT to the head and neck were observed. Additional toxicities attributable to G-CSF and/or daily injections were as follows: elevated WBC requiring G-CSF dose reduction by prospectively planned guidelines occurred in nine patients in the G-CSF arm; grade 2-3 bone pain was observed in two patients in the G-CSF arm; three patients refused injection (2 G-CSF, 1 placebo)"

G-CSF = granulocyte-colony stimulating factor.

Table 5. Adverse events: EGF

Study ID	Adverse events results
Kim 2017	"Adverse events were similar in both groups (Table 3). The most common adverse event in the rhEGF group was nausea (n = 7, 10.4%). The incidence of other adverse events including oral pain, dry mouth, and taste alteration was low. All the adverse events were mild and transient. No grade 3 or 4 adverse events were noted during the study period" (there were no differences between groups in any adverse event)
Wu 2009	"The frequency of minor and serious adverse events was similar in all groups. Most adverse events were related to primary disease status and treatment modalities"

EGF = epidermal growth factor.

Table 6. Adverse events: ITF

Study ID	Adverse events results
Peterson 2009	"Only a minority of patients (six [6.1%] of 99 patients) reported mild to moderate treatment-emergent adverse events on the study. The symptoms included abdominal pain, diarrhea, oral pain, headache, and hypertension (Table 2). Of these, four were considered related to study drug: one (3%) was in the placebo group, two (6%) were in the low-dose rhITF group, and one (3%) was in the high-dose rhITF group. The events were isolated and resolved

Table 6. Adverse events: ITF (Continued)

	spontaneously without sequelae”
--	---------------------------------

ITF = intestinal trefoil factor.

Table 7. TGF-beta(2) versus placebo

Study ID	Population	Outcome	TGF-beta(2)	Placebo	Result
Antoun 2009	CT alone for colorectal cancer	Oral mucositis (WHO 0 to 4 scale); any oral mucositis	0/9	2/4	RR 0.10 (95% CI 0.01 to 1.71); P = 0.11

CI = confidence interval; CT = chemotherapy; RR = risk ratio; TGF = transforming growth factor; WHO = World Health Organization.

APPENDICES

Appendix I. Cochrane Oral Health’s Trials Register search strategy

- 1 ((neoplasm* or cancer* or leukaemi* or leukemia* or tumour* or tumor* or malignan* or neutropeni* or neutropenia* or carcino* or adenocarcinoma* or lymphoma*):ti,ab) AND (INREGISTER)
- 2 ((radioth* or radiat* or irradiat*):ti,ab) AND (INREGISTER)
- 3 (((“bone marrow” and transplant*) or “hematopoietic stem cell transplant*” or “haematopoietic stem cell transplant*” or HSCT):ti,ab) AND (INREGISTER)
- 4 (chemo*:ti,ab) AND (INREGISTER)
- 5 (#1 or #2 or #3 or #4) AND (INREGISTER)
- 6 ((stomatitis or mucositis):ti,ab) AND (INREGISTER)
- 7 ((oral and mucos*):ti,ab) AND (INREGISTER)
- 8 ((mycosis or mycotic):ti,ab) AND (INREGISTER)
- 9 (mIAS:ti,ab) AND (INREGISTER)
- 10 (#6 or #7 or #8 or #9) AND (INREGISTER)
- 11 ((“growth factor*” or “growth substance*” or “immunologic factor*”):ti,ab) AND (INREGISTER)
- 12 (“fibroblast growth factor*”:ti,ab) AND (INREGISTER)
- 13 ((keratinocyte* or cytokine*):ti,ab) AND (INREGISTER)
- 14 ((palifermin* or KGF or FGF):ti,ab) AND (INREGISTER)
- 15 ((keprivance or velafermin or repifermin):ti,ab) AND (INREGISTER)
- 16 (glycoprotein*:ti,ab) AND (INREGISTER)
- 17 ((colony-stimulat* or “macrophage-granulocyte inducer*” or “myeloid cell-growth inducer*” or “protein inducer MGI”):ti,ab) AND (INREGISTER)
- 18 ((GM-CSF or G-CSF):ti,ab) AND (INREGISTER)
- 19 ((molgramostim or Growgen-GM or Leucamax or Molcass or Gramostim or Leucocitim or Mielogen or Meustim or Bagomol or Gramal):ti,ab) AND (INREGISTER)
- 20 ((rhEGF or “recombinant epithelial growth factor*” or “epidermal growth factor*” or EGF):ti,ab) AND (INREGISTER)
- 21 ((“platelet-derived growth factor*” or PDGF or “platelet lysate”):ti,ab) AND (INREGISTER)

22 (“transforming growth factor*” or “bone-derived transforming growth factor*” or “milk growth factor*” or “platelet transforming growth factor*” or TGF-beta or TGFβ):ti,ab) AND (INREGISTER)

23 (“hepatocyte growth factor*” or hepatopoietin or “scatter factor”):ti,ab) AND (INREGISTER)

24 ((somatomedin* or “insulin-like growth factor*” or “sulfation factor*” or Mecasermin or Increlex or Iplex or IGF-1 or IGF1):ti,ab) AND (INREGISTER)

25 (erythropoietin*:ti,ab) AND (INREGISTER)

26 ((thrombopoietin* or “mpl Ligand” or “megakaryocyte colony stimulating factor*” or “megakaryocyte growth and development factor*” or “MGDF factor” or “myeloproliferative leukemia virus oncogene ligand” or “thrombocytopoiesis-stimulating factor” or thrombocytopoietin*):ti,ab) AND (INREGISTER)

27 (“interleukin 11” or “adipogenesis inhibitory factor*” or IL-11 or IL11):ti,ab) AND (INREGISTER)

28 ((ghrelin* or “GHRL protein” or obestatin):ti,ab) AND (INREGISTER)

29 ((ATL-104 or ATL104):ti,ab) AND (INREGISTER)

30 ((whey or “milk derived protein” or “milk derived growth factor”):ti,ab) AND (INREGISTER)

31 (“glucagon-like peptide 2” or “amino acid*” or proglucagon or GLP-2 or teduglutide or Gattex or Revestive):ti,ab) AND (INREGISTER)

32 (“trefoil factor” or “carcinoembryonic antigen cell adhesion molecule 1” or glutathione or isethion):ti,ab) AND (INREGISTER)

33 (“vascular endothelial growth factor*” or VEGF*):ti,ab) AND (INREGISTER)

34 (“targeted therap*” or “targeted agent*”):ti,ab) AND (INREGISTER)

35 (“biologic* therap*”:ti,ab) AND (INREGISTER)

36 ((#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35)) AND (INREGISTER)

37 (#5 and #10 and #36) AND (INREGISTER)

Appendix 2. Cochrane Central Register of Controlled Clinical Trials (CENTRAL) search strategy

#1 [mh neoplasms]

#2 [mh radiotherapy]

#3 [mh “antineoplastic agents”]

#4 [mh “bone marrow transplantation”]

#5 [mh “hematopoietic stem cell transplantation”]

#6 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees

#7 (neoplasm* or cancer* or leukaemi* or leukemi* or tumour* or tumor* or malignan* or neutropeni* or neutropeni* or carcino* or adenocarcinoma* or lymphoma*)

#8 (radioth* or radiat* or irradiat*)

#9 (“bone marrow” and transplant*) or “hematopoietic stem cell transplant*” or “haematopoietic stem cell transplant*” or HSCT)

#10 chemo*

#11 {or #1-#10}

#12 [mh Stomatitis]

#13 [mh “oral candidiasis”]

#14 stomatitis

#15 mucositis

#16 (oral near/6 mucos*)

#17 (mycosis or mycotic)

#18 mIAS

#19 {or #12-#18}

#20 (“growth factor*” or “growth substance*” or “immunologic factor*”)

#21 [mh “Fibroblast growth factor 7”]

#22 “fibroblast growth factor*”

#23 (keratinocyte* or cytokine*)

#24 (palifermin* or KGF or FGF)

#25 (keprivance or velafermin or repifermin)

#26 glycoprotein*

#27 [mh "colony-stimulating factors"]
 #28 (colony-stimulat* or "macrophage-granulocyte inducer*" or "myeloid cell-growth inducer*" or "protein inducer MGI")
 #29 (GM-CSF or G-CSF)
 #30 (molgramostim or Growgen-GM or Leucomax or Molcass or Gramostim or Leucocitim or Mielogen or Meustim or Bagomol or Gramal)
 #31 [mh ^"Epidermal growth factor"]
 #32 (rhEGF or "recombinant epithelial growth factor*" or "epidermal growth factor*" or EGF)
 #33 [mh ^"Platelet-derived growth factor"]
 #34 ("platelet-derived growth factor*" or PDGF or "platelet lysate")
 #35 [mh ^"Transforming growth factor beta"]
 #36 ("transforming growth factor*" or "bone-derived transforming growth factor*" or "milk growth factor*" or "platelet transforming growth factor*" or TGF-beta or TGFBeta)
 #37 [mh ^"Hepatocyte growth factor"]
 #38 ("hepatocyte growth factor*" or hepatopoietin or "scatter factor")
 #39 [mh Somatomedin]
 #40 (somatomedin* or "insulin-like growth factor*" or "sulfation factor*" or Mecasermin or Increlex or Iplex or IGF-1 or IGF1)
 #41 erythropoietin*
 #42 [mh ^Thrombopoietin]
 #43 (thrombopoietin* or "mpl Ligand" or "megakaryocyte colony stimulating factor*" or "megakaryocyte growth and development factor*" or "MGDF factor" or "myeloproliferative leukemia virus oncogene ligand" or "thrombocytopoiesis-stimulating factor" or thrombocytopoietin*)
 #44 [mh ^Ghrelin]
 #45 [mh "Interleukin 11"]
 #46 ("interleukin 11" or "adipogenesis inhibitory factor*" or IL-11 or IL11)
 #47 (ghrelin* or "GHRL protein" or obestatin)
 #48 (ATL-104 or ATL104)
 #49 (whey or ("milk derived" next (protein or "growth factor")))
 #50 [mh ^"Glucagon-like peptide 2"]
 #51 ("glucagon-like peptide 2" or "amino acid*" or proglucagon or GLP-2 or teduglutide or Gattex or Revestive)
 #52 [mh ^Glutathione]
 #53 ("trefoil factor" or "carcinoembryonic antigen cell adhesion molecule 1" or glutathione or isethion)
 #54 [mh ^"Vascular endothelial growth factors"]
 #55 ("vascular endothelial growth factor*" or VEGF*)
 #56 [mh ^"Molecular targeted therapy"]
 #57 (targeted near/3 (therap* or agent*))
 #58 (biologic* next therap*)
 #59 {or #20-#58}
 #60 #11 and #19 and #59

Appendix 3. MEDLINE Ovid search strategy

1. exp NEOPLASMS/
2. exp RADIOTHERAPY/
3. exp Antineoplastic agents/
4. Anti-neoplastic combined chemotherapy protocols/
5. Bone Marrow Transplantation/
6. Hematopoietic Stem Cell Transplantation/
7. (neoplasm\$ or cancer\$ or leukaemi\$ or leukemia\$ or tumour\$ or tumor\$ or malignan\$ or neutropeni\$ or carcino\$ or adenocarcinoma\$ or lymphoma\$).ti,ab.
8. (radioth\$ or radiat\$ or irradiat\$).ti,ab.
9. ((bone adj marrow adj5 transplant\$) or "hematopoietic stem cell transplant\$" or "haematopoietic stem cell transplant\$" or HSCT).ti,ab.

10. chemo\$.ti,ab.
11. or/1-10
12. exp STOMATITIS/
13. Candidiasis, Oral/
14. stomatitis.ti,ab.
15. mucositis.ti,ab.
16. (oral adj6 mucos\$).ti,ab.
17. (mycosis or mycotic).ti,ab.
18. mIAS.ti,ab.
19. or/12-18
20. ((growth adj factor\$) or (growth adj substance\$) or (immunologic adj factor\$)).ti,ab.
21. Fibroblast growth factor 7/
22. "fibroblast growth factor\$.ti,ab.
23. (keratinocyte\$ or cytokine\$).ti,ab.
24. (palifermin\$ or KGF or FGF).ti,ab.
25. (kepivance or velafermin or repifermin).ti,ab.
26. glycoprotein\$.ti,ab.
27. exp Colony-stimulating factors/
28. ("colony-stimulat\$" or "macrophage-granulocyte inducer\$" or "myeloid cell-growth inducer\$" or "protein inducer MGI").ti,ab.
29. (GM-CSF or G-CSF).ti,ab.
30. (molgramostim or Growgen-GM or Leucomax or Molcass or Gramostim or Leucocitim or Mielogen or Meustim or Bagomol or Gramal).ti,ab.
31. Epidermal growth factor/
32. (rhEGF or "recombinant epithelial growth factor\$" or "epidermal growth factor\$" or EGF).ti,ab.
33. Platelet-derived growth factor/
34. ("platelet-derived growth factor\$" or PDGF or "platelet lysate").ti,ab.
35. Transforming Growth Factor beta/
36. ("transforming growth factor\$" or "bone-derived transforming growth factor\$" or "milk growth factor\$" or "platelet transforming growth factor" or TGF-beta or TGFbeta).ti,ab.
37. Hepatocyte growth factor/
38. ("hepatocyte growth factor\$" or hepatopoietin or "scatter factor").ti,ab.
39. exp Somatomedin/
40. (somatomedin\$ or "insulin-like growth factor\$" or "sulfation factor" or Mecasermin or Increlex or Iplex or IGF-1 or IGF1).ti,ab.
41. erythropoietin\$.ti,ab.
42. Thrombopoietin/
43. (thrombopoietin\$ or "mpl Ligand" or "megakaryocyte colony stimulating factor\$" or "megakaryocyte growth and development factor\$" or "MGDF factor" or "myeloproliferative leukemia virus oncogene ligand" or "thrombocytopoiesis-stimulating factor" or thrombocytopoietin\$).ti,ab.
44. Ghrelin/
45. Interleukin 11/
46. ("interleukin 11" or "Adipogenesis Inhibitory Factor\$" or IL-11 or IL11).ti,ab.
47. (ghrelin\$ or "GHRL protein" or obestatin).ti,ab.
48. (ATL-104 or ATL104).ti,ab.
49. (whey or ("milk derived" adj (protein or growth factor))).ti,ab.
50. Glucagon-Like Peptide 2/
51. ("glucagon-like peptide 2" or (amino adj acid\$) or proglucagon or GLP-2 or teduglutide or Gattex or Revestive).ti,ab.
52. Glutathione/
53. ("trefoil factor" or "carcinoembryonic antigen cell adhesion molecule 1" or glutathione or isethion).ti,ab.
54. Vascular endothelial growth factors/
55. ("vascular endothelial growth factor\$" or VEGF\$).ti,ab.
56. Molecular targeted therapy/
57. (targeted adj3 (therap\$ or agent\$)).ti,ab.
58. (biologic\$ adj therap\$).ti,ab.

59. or/20-58

60. 11 and 19 and 59

The above subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials (RCTs) in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) ([Higgins 2011](#)).

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. drug therapy.fs.

6. randomly.ab.

7. trial.ab.

8. groups.ab.

9. or/1-8

10. exp animals/ not humans.sh.

11. 9 not 10

Appendix 4. Embase Ovid search strategy

1. exp NEOPLASM/

2. exp RADIOTHERAPY/

3. exp Antineoplastic agent/

4. Bone Marrow Transplantation/

5. Hematopoietic Stem Cell Transplantation/

6. (neoplasm\$ or cancer\$ or leukaemi\$ or leukemia\$ or tumour\$ or tumor\$ or malignan\$ or neutropeni\$ or carcino\$ or adenocarcinoma\$ or lymphoma\$).ti,ab.

7. (radioth\$ or radiat\$ or irradiat\$).ti,ab.

8. ((bone adj marrow adj5 transplant\$) or "hematopoietic stem cell transplant\$" or "haematopoietic stem cell transplant\$" or HSCT).ti,ab.

9. chemo\$.ti,ab.

10. or/1-9

11. exp STOMATITIS/

12. Thrush/

13. stomatitis.ti,ab.

14. mucositis.ti,ab.

15. (oral adj6 mucos\$).ti,ab.

16. (mycosis or mycotic).ti,ab.

17. mIAS.ti,ab.

18. or/11-17

19. ((growth adj factor\$) or (growth adj substance\$) or (immunologic adj factor\$)).ti,ab.

20. "fibroblast growth factor\$.ti,ab.

21. (keratinocyte\$ or cytokine\$).ti,ab.

22. (palifermin\$ or KGF or FGF).ti,ab.

23. (kepivance or velafermin or repifermin).ti,ab.

24. glycoprotein\$.ti,ab.

25. exp Colony-stimulating factor/

26. ("colony-stimulat\$" or "macrophage-granulocyte inducer\$" or "myeloid cell-growth inducer\$" or "protein inducer MGI").ti,ab.

27. (GM-CSF or G-CSF).ti,ab.

28. (molgramostim or Growgen-GM or Leucomax or Molcass or Gramostim or Leucocitim or Mielogen or Meustim or Bagomol or Gramal).ti,ab.

29. Epidermal growth factor/

30. (rhEGF or "recombinant epithelial growth factor\$" or "epidermal growth factor\$" or EGF).ti,ab.

31. Platelet derived growth factor/
 32. ("platelet-derived growth factor\$" or PDGF or "platelet lysate").ti,ab.
 33. Transforming Growth Factor beta/
 34. ("transforming growth factor\$" or "bone-derived transforming growth factor\$" or "milk growth factor\$" or "platelet transforming growth factor" or TGF-beta or TGFbeta).ti,ab.
 35. Scatter factor/
 36. ("hepatocyte growth factor\$" or hepatopoietin or "scatter factor").ti,ab.
 37. exp Somatomedin/
 38. (somatomedin\$ or "insulin-like growth factor\$" or "sulfation factor" or Mecasermin or Increlex or Iplex or IGF-1 or IGF1).ti,ab.
 39. erythropoietin\$.ti,ab.
 40. Thrombopoietin/
 41. (thrombopoietin\$ or "mpl Ligand" or "megakaryocyte colony stimulating factor\$" or "megakaryocyte growth and development factor\$" or "MGDF factor" or "myeloproliferative leukemia virus oncogene ligand" or "thrombocytopoiesis-stimulating factor" or thrombocytopoietin\$).ti,ab.
 42. Ghrelin/
 43. Interleukin 11/
 44. ("interleukin 11" or "Adipogenesis Inhibitory Factor\$" or IL-11 or IL11).ti,ab.
 45. (ghrelin\$ or "GHRL protein" or obestatin).ti,ab.
 46. (ATL-104 or ATL104).ti,ab.
 47. (whey or ("milk derived" adj (protein or growth factor))).ti,ab.
 48. ("glucagon-like peptide 2" or (amino adj acid\$) or proglucagon or GLP-2 or teduglutide or Gattex or Revestive).ti,ab.
 49. Glutathione/
 50. ("trefoil factor" or "carcinoembryonic antigen cell adhesion molecule 1" or glutathione or isethion).ti,ab.
 51. Vasculotropin/
 52. ("vascular endothelial growth factor\$" or VEGF\$).ti,ab.
 53. Molecularly targeted therapy/
 54. (targeted adj3 (therap\$ or agent\$)).ti,ab.
 55. (biologic\$ adj therap\$).ti,ab.
 56. or/19-55
 57. 10 and 18 and 56
- The above subject search was linked to adapted version of the Cochrane Embase Project filter for identifying RCTs in EMBASE via OVID (see www.cochranelibrary.com/help/central-creation-details.html for information).
1. Randomized controlled trial/
 2. Controlled clinical study/
 3. Random\$.ti,ab.
 4. randomization/
 5. intermethod comparison/
 6. placebo.ti,ab.
 7. (compare or compared or comparison).ti.
 8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
 9. (open adj label).ti,ab.
 10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab
 11. double blind procedure/
 12. parallel group\$1.ti,ab.
 13. (crossover or cross over).ti,ab.
 14. ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab.
 15. (assigned or allocated).ti,ab.
 16. (controlled adj7 (study or design or trial)).ti,ab.
 17. (volunteer or volunteers).ti,ab.
 18. trial.ti.
 19. or/1-18
 20. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

Appendix 5. CINAHL EBS CO (Cumulative Index to Nursing and Allied Health Literature) search strategy

S53 S10 and S18 and S52
S52 S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51
S51 (biologic* N1 therap*)
S50 (targeted N3 (therap* or agent*))
S49 ("vascular endothelial growth factor*" or VEGF*)
S48 (mh Vascular endothelial growth factors)
S47 ("trefoil factor" or "carcinoembryonic antigen cell adhesion molecule 1" or glutathione or isethion)
S46 (mh Glutathione)
S45 ("glucagon-like peptide 2" or "amino acid*" or proglucagon or GLP-2 or teduglutide or Gattex or Revestive)
S44 (mh Glucagon-like peptide 2)
S43 (whey or ("milk derived" N1 (protein or "growth factor")))
S42 (ATL-104 or ATL104)
S41 (ghrelin* or "GHRL protein" or obestatin)
S40 ("interleukin 11" or "adipogenesis inhibitory factor*" or IL-11 or IL11)
S39 (mh Ghrelin)
S38 (thrombopoietin* or "mpl Ligand" or "megakaryocyte colony stimulating factor*" or "megakaryocyte growth and development factor*" or "MGDF factor" or "myeloproliferative leukemia virus oncogene ligand" or "thrombocytopoiesis-stimulating factor" or thrombocytopoietin*)
S37 erythropoietin*
S36 (somatomedin* or "insulin-like growth factor*" or "sulfation factor*" or Mecasermin or Increlex or Iplex or IGF-1 or IGF1)
S35 ("hepatocyte growth factor*" or hepatopoietin or "scatter factor")
S34 ("transforming growth factor*" or "bone-derived transforming growth factor*" or "milk growth factor*" or "platelet transforming growth factor*" or TGF-beta or TGFBeta)
S33 (mh Transforming growth factor beta)
S32 ("platelet-derived growth factor*" or PDGF or "platelet lysate")
S31 (mh Platelet-derived growth factor)
S30 (rhEGF or "recombinant epithelial growth factor*" or "epidermal growth factor*" or EGF)
S29 (MH "Epidermal Growth Factors")
S28 (molgramostim or Growgen-GM or Leucomax or Molcass or Gramostim or Leucocitim or Mielogen or Meustim or Bagomol or Gramal)
S27 (GM-CSF or G-CSF)
S26 (colony-stimulat* or "macrophage-granulocyte inducer*" or "myeloid cell-growth inducer*" or "protein inducer MGI")
S25 (mh colony-stimulating factors)
S24 glycoprotein*
S23 (keprivance or velafermin or repifermin)
S22 (palifermin* or KGF or FGF)
S21 (keratinocyte* or cytokine*)
S20 "fibroblast growth factor*"
S19 ("growth factor*" or "growth substance*" or "immunologic factor*")
S18 S11 or S12 or S13 or S14 or S15 or S16 or S17
S17 mIAS
S16 (mycosis or mycotic)
S15 (oral N6 mucos*)
S14 mucositis
S13 stomatitis
S12 (MH "Candidiasis, Oral")

S11 (mh stomatitis+)

S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9

S9 chemo*

S8 (“bone marrow” and transplant*) or “hematopoietic stem cell transplant*” or “haematopoietic stem cell transplant*” or HSCT)

S7 (radioth* or radiat* or irradiat*)

S6 (neoplasm* or cancer* or leukaemi* or leukemia* or tumour* or tumor* or malignan* or neutropeni* or neutropeni* or carcino* or adenocarcinoma* or lymphoma*)

S5 (mh hematopoietic stem cell transplantation)

S4 (mh bone marrow transplantation)

S3 (mh antineoplastic agents+)

S2 (mh radiotherapy+)

S1 (mh neoplasms+)

The above subject search was linked to Cochrane Oral Health’s filter for CINAHL via EBSCO.

S1 MH Random Assignment or MH Single-blind Studies or MH Double-blind Studies or MH Triple-blind Studies or MH Crossover design or MH Factorial Design

S2 TI (“multicentre study” or “multicenter study” or “multi-centre study” or “multi center study”) or AB (“multicentre study” or “multicenter study” or “multi centre study” or “multi-center study”) or SU (“multicentre study” or “multicenter study” or “multi-centre study” or “multi-center study”)

S3 TI random* or AB random*

S4 AB “latin square” or TI “latin square”

S5 TI (crossover or cross-over) or AB (crossover or cross-over) or SU (crossover or cross-over)

S6 MH Placebos

S7 AB (singl* or doubl* or trebl* or tripl*) or TI (singl* or doubl* or trebl* or tripl*)

S8 TI blind* or AB mask* or AB blind* or TI mask*

S9 S7 and S8

S10 TI Placebo* or AB Placebo* or SU Placebo*

S11 MH Clinical Trials

S12 TI (Clinical AND Trial) or AB (Clinical AND Trial) or SU (Clinical AND Trial)

S13 S1 or S2 or S3 or S4 or S5 or S6 or S9 or S10 or S11 or S12

Appendix 6. CANCERLIT PubMed search strategy

We searched CANCERLIT by limiting a PubMed search with the Cancer subject filter and the following search strategy.

#60 (#11 and #19 and #59)

#59 (#20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58)

#58 “biologic* therap*”

#57 (“targeted therap*” or “targeted agent*”)

#56 Molecular targeted therapy [mh:noexp]

#55 (“vascular endothelial growth factor*” or VEGF*)

#54 Vascular endothelial growth factors [mh:noexp]

#53 (“trefoil factor” or “carcinoembryonic antigen cell adhesion molecule 1” or glutathione or isethion))

#52 Glutathione [mh:noexp]

#51 (“glucagon-like peptide 2” or “amino acid*” or proglucagon or GLP-2 or teduglutide or Gattex or Revestive))

#50 Glucagon-like peptide 2 [mh:noexp]

#49 ((whey or “milk derived protein” or “milk derived growth factor”))

#48 ((ATL-104 or ATL104))

#47 ((ghrelin* or “GHRL protein” or obestatin))

#46 ((“interleukin 11” or “adipogenesis inhibitory factor*” or IL-11 or IL11))

#45 Interleukin 11 [mh:exp]

#44 Ghrelin [mh:noexp]

#43 ((thrombopoietin* or “mpl Ligand” or “megakaryocyte colony stimulating factor*” or “megakaryocyte growth and development factor*” or “MGDF factor” or “myeloproliferative leukemia virus oncogene ligand” or “thrombocytopoiesis-stimulating factor” or thrombocytopoietin*))

#42 Thrombopoietin [mh:noexp]

#41 erythropoietin*

#40 ((somatomedin* or “insulin-like growth factor*” or “sulfation factor*” or Mecasermin or Increlex or Iplex or IGF-1 or IGF1))

#39 Somatomedin [mh:exp]

#38 ((“hepatocyte growth factor*” or hepatopoietin or “scatter factor”))

#37 Hepatocyte growth factor [mh:noexp]

#36 ((“transforming growth factor*” or “bone-derived transforming growth factor*” or “milk growth factor*” or “platelet transforming growth factor*” or TGF-beta or TGFBeta))

#35 Transforming growth factor beta [mh:noexp]

#34 ((“platelet-derived growth factor*” or PDGF or “platelet lysate”))

#33 Platelet-derived growth factor [mh:noexp]

#32 ((rhEGF or “recombinant epithelial growth factor*” or “epidermal growth factor*” or EGF))

#31 Epidermal growth factor [mh:noexp]

#30 ((molgramostim or Growgen-GM or Leucomax or Molcass or Gramostim or Leucocitim or Mielogen or Meustim or Bagomol or Gramal))

#29 ((GM-CSF or G-CSF))

#28 ((colony-stimulat* or “macrophage-granulocyte inducer*” or “myeloid cell-growth inducer*” or “protein inducer MGI”))

#27 colony-stimulating factors [mh:exp]

#26 glycoprotein*

#25 ((keprivance or velafermin or repifermin))

#24 ((palifermin* or KGF or FGF))

#23 ((keratinocyte* or cytokine*))

#22 “fibroblast growth factor*”

#21 Fibroblast growth factor 7 [mh:noexp]

#20 ((“growth factor*” or “growth substance*” or “immunologic factor”))

#19 (#12 or #13 or #14 or #15 or #16 or #17 or #18)

#18 mIAS

#17 ((mycosis or mycotic))

#16 “oral mucos*”

#15 mucositis

#14 stomatitis

#13 oral candidiasis [mh:noexp]

#12 Stomatitis [mh:exp]

#11 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)

#10 chemo*

#9 (((“bone marrow” and transplant*) or “hematopoietic stem cell transplant*” or “haematopoietic stem cell transplant*” or HSCT))

#8 ((radioth* or radiat* or irradiat*))

#7 ((neoplasm* or cancer* or leukaemi* or leukemia* or tumour* or tumor* or malignan* or neutropeni* or neutropeni* or carcino* or adenocarcinoma* or lymphoma*))

#6 Antineoplastic Combined Chemotherapy Protocols [mh:noexp]

#5 “hematopoietic stem cell transplantation” [mh:noexp]

#4 bone marrow transplantation [mh:noexp]

#3 antineoplastic agents [mh:exp]

#2 radiotherapy [mh:exp]

#1 neoplasms [mh:exp]

This search was linked with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.a of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) ([Lefebvre 2011](#)).

#1 randomized controlled trial [pt]

#2 controlled clinical trial [pt]

#3 randomized [tiab]
 #4 placebo [tiab]
 #5 drug therapy [sh]
 #6 randomly [tiab]
 #7 trial [tiab]
 #8 groups [tiab]
 #9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
 #10 animals [mh] not humans [mh]
 #11 #9 NOT #10

Appendix 7. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) search strategy

oral mucositis and cytokines
 oral mucositis and growth factor
 oral mucositis and palifermin
 oral mucositis and GM-CSF

Appendix 8. World Health Organization International Clinical Trials Registry Platform search strategy

oral mucositis and cytokines
 oral mucositis and growth factor
 oral mucositis and palifermin
 oral mucositis and GM-CSF

Appendix 9. Oral mucositis measurement scales

Oral mucositis assessment scale (OMAS)

(as reported in [Freytes 2004](#))

Oral cavity ulceration		Oral cavity erythema	
Grade 0	No lesion	Grade 0	None
Grade 1	Lesion < 1 cm ²	Grade 1	Not severe
Grade 2	Lesion 1 cm ² to 3 cm ²	Grade 2	Severe
Grade 3	Lesion > 3 cm ²	-	-

Ulceration and erythema are measured at 9 different sites (upper and lower labial mucosa, right and left buccal mucosa, right and left lateral and ventral portions of the tongue, floor of the mouth, soft palate (faucis), and hard palate (gingival)) and summated to give a total mucositis score. Therefore score could range from 0 to 45.

Radiation Therapy Oncology Group (RTOG) scale

(physician-rated objective gross score as reported in [Chi 1995](#))

Grade 0	None
Grade 1	Erythematous sores
Grade 2	Patchy mucositis (< 1/2 mucosa)
Grade 3	Confluent fibrinous mucositis (> 1/2 mucosa)
Grade 4	Haemorrhage and necrosis

Radiation Therapy Oncology Group (RTOG) scale

(as reported in [Wu 2009](#))

Grade 0	None
Grade 1	Injection; may experience mild pain not requiring analgesia
Grade 2	Patchy mucositis that may produce an inflammatory serosanguineous discharge; may experience moderate pain requiring analgesia
Grade 3	Confluent fibrinous mucositis; may include severe pain requiring narcosis
Grade 4	Ulceration, haemorrhage, or necrosis

Cancer and Leukemia Group B (CALGB) scale

(as reported in [Turhal 2000](#))

Grade 0	No mucositis
Grade 1	Painless ulcers, erythema or mild soreness
Grade 2	Painful erythema, edema, or ulcers, but can eat
Grade 3	Painful erythema, edema, or ulcers, and cannot eat
Grade 4	Requires parenteral or enteral support

National Cancer Institute common toxicity criteria (NCI-CTC)

(as reported in [Dazzi 2003](#))

Grade 0	No mucositis
Grade 1	Painless ulcers, erythema or mild soreness in the absence of lesions
Grade 2	Painful erythema, edema or ulcers, but can eat or swallow
Grade 3	Painful erythema, edema or ulcers requiring intravenous hydration
Grade 4	Severe ulceration or requires parenteral or enteral nutritional support

World Health Organization (WHO) scale

(as reported in [Vadhan-Raj 2010](#))

Grade 0	No mucositis
Grade 1	Soreness ± erythema
Grade 2	Erythema, ulcers. Patient can swallow solid diet
Grade 3	Ulcers, extensive erythema. Patient cannot swallow solid diet
Grade 4	Mucositis to the extent that alimentation is not possible

HISTORY

Protocol first published: Issue 12, 2015

Review first published: Issue 11, 2017

Date	Event	Description
26 January 2016	Amended	Minor edit (hyperlink)

CONTRIBUTIONS OF AUTHORS

Philip Riley: writing the Background and Methods sections, screening searches, data extraction, risk of bias assessment, interpreting the results, writing the review.

Anne-Marie Glenny: writing the Methods section, screening searches, data extraction, risk of bias assessment, interpreting the results.

Helen V Worthington: writing the Methods section, screening searches, data extraction, risk of bias assessment, interpreting the results.

Anne Littlewood: writing the Methods section, designing the search strategy and carrying out the searches, screening searches, data extraction, risk of bias assessment, interpreting the results.

Luisa M Fernandez Mauleffinch: writing the Methods section, screening searches, data extraction, risk of bias assessment, interpreting the results, copy editing the review.

Jan E Clarkson: interpreting the results and providing a clinical perspective.

Martin G McCabe: interpreting the results and providing a clinical perspective.

DECLARATIONS OF INTEREST

There was no industry funding to support the undertaking of this Cochrane Review.

Philip Riley: I am a salaried member of the Cochrane Oral Health editorial team.

Anne-Marie Glenny: none known. I am Deputy Co-ordinating Editor of Cochrane Oral Health.

Helen V Worthington: none known. I am Co-ordinating Editor of Cochrane Oral Health.

Anne Littlewood: I am a salaried member of the Cochrane Oral Health editorial team.

Luisa M Fernandez Mauleffinch: I am a salaried member of the Cochrane Oral Health editorial team.

Jan E Clarkson: none known. I am Co-ordinating Editor of Cochrane Oral Health.

Martin G McCabe: none known. I am an Editor with Cochrane Oral Health.

SOURCES OF SUPPORT

Internal sources

- School of Dentistry, The University of Manchester, UK.
- Manchester Academic Health Sciences Centre (MAHSC) and the NIHR Manchester Biomedical Research Centre, UK.

External sources

- National Institute for Health Research (NIHR), UK.

This project was supported by the NIHR, via Cochrane Infrastructure funding to Cochrane Oral Health. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, the NIHR, the NHS or the Department of Health.

- Cochrane Oral Health Global Alliance, Other.

The production of Cochrane Oral Health reviews has been supported financially by our Global Alliance since 2011 (oralhealth.cochrane.org/partnerships-alliances). Contributors over the past year have been the American Association of Public Health Dentistry, USA; the British Association for the Study of Community Dentistry, UK; the British Society of Paediatric Dentistry, UK; the Canadian Dental Hygienists Association, Canada; the Centre for Dental Education and Research at All India Institute of Medical Sciences, India; the National Center for Dental Hygiene Research & Practice, USA; New York University College of Dentistry, USA; NHS Education for Scotland, UK; and the Swiss Society for Endodontology, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- For the 'Summary of findings' tables, we decided to limit the outcomes to the incidence of moderate to severe, and the incidence of severe oral mucositis, and also adverse events. This was partly because the scales used to assess oral mucositis often incorporate aspects of some of the secondary outcomes, and it is the most clinically relevant outcome, and partly because the tables would become unwieldy and difficult to read once the secondary outcomes had been divided into their subgroups based on cancer treatment type. We also eliminated the incidence of any oral mucositis from the tables because ulcerative and severe grades are more important.
- We decided not to report data from secondary outcomes that were not suitable for meta-analysis in additional tables as we felt that this would not be helpful and could result in 'vote-counting' i.e. xx studies reported a difference and yy studies reported no difference.